LUTONIX® DRUG COATED BALLOON PTA CATHETER

PMA P130024

FOR TREATMENT OF STENOTIC OR OBSTRUCTIVE LESIONS IN THE FEMOROPOPLITEAL ARTERY

SPONSOR EXECUTIVE SUMMARY

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ABI	Ankle-brachial index
ACC/AHA	American College of Cardiology/American Heart Association
AE	Adverse Event
AFS	Amputation Free Survival
API	Active Pharmaceutical Ingredient
ASTM	American Standard Test Method
BMS	Bare Metal Stent
CEC	Clinical Events Committee
CI	Confidence Interval
CLI	Critical Limb Ischemia (Rutherford Class 4, 5 or 6)
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Curriculum vitae
DCB	Drug Coated Balloon
DES	Drug-eluting Stent
DMC	Data Monitoring Committee
DS	Diameter Stenosis (%DS, Percent Diameter Stenosis)
DUS	Duplex Ultrasound
EC	Ethics Committee
eCRF	Electronic Case Report Form
EQ-5D	Euro-Qol 5-Dimension Questionnaire
EU	European Union
FDA	Food and Drug Administration
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ITT	Intent to Treat
MLD	Minimal Lumen Diameter
OTW	Over-the-Wire
OUS	Outside the US
PAD	Peripheral Artery Disease
PSV	Peak Systolic Velocity
PSVR	Peak Systolic Velocity Ratio
PTA	Percutaneous Transluminal Angioplasty
QOL	Quality of Life
QVA	Quantitative Vascular Angiography (an x-ray based imaging useful for assessing vascular anatomy)
RCT	Randomized Controlled Trial
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SFA	Superficial Femoral Artery
SF-36	Short-form 36 Questionnaire Version 2
SFA	Superficial Femoropopliteal Artery

TL	Target Lesion
TLR	Target Lesion Revascularization (any intervention affecting the analysis segment, including 10 mm proximal and distal to the treated segment)
TV	Target Vessel
TVR	Target Vessel Revascularization (any intervention affecting the target vessel)
UADE	Unanticipated Adverse Device Effect
US	United States
VIVA	Vascular Interventional Advances Organization
WIQ	Walking Impairment Questionnaire

1 EXECUTIVE SUMMARY

The Lutonix Drug Coated Balloon (DCB) PTA Catheter (Lutonix DCB) is a 0.035 inch guidewire-compatible, over the wire (OTW) catheter with a paclitaxel coating on the balloon surface. The Lutonix DCB is intended to dilate stenotic or obstructive lesions in the femoropopliteal artery (SFA) to improve limb perfusion. The proposed indication is as follows:

> *The LUTONIX® 035 Drug Coated Balloon PTA Catheter is indicated for improving luminal diameter for the treatment of obstructive de novo or non-stented restenotic lesions (≤ 15 cm in length) in native femoropopliteal arteries having reference vessel diameters of 4 mm to 6 mm.*

The femoropopliteal artery is the most commonly diseased vessel in the peripheral circulation. Restricted blood flow causes symptoms including intermittent claudication, rest pain, and ischemic ulcers that may progress to gangrene and limb loss. The goal of percutaneous treatment is to restore vessel patency, but restenosis after angioplasty (PTA) is common. Bare metal and drug eluting stents were introduced to improve vessel patency. Patency after stenting is more durable, but certain vessel areas are not appropriate for stenting, and implantation of a foreign body limits future treatment options. There is a clinical need for a device that is able to achieve more durable patency than PTA without leaving a permanent implant.

In an effort to address that unmet need, development of Lutonix DCB began in 2007. In close collaboration with FDA, a thorough panel of biocompatibility, bench, and animal testing was performed based on international standards and FDA guidance. Results from these combined studies demonstrated functionality and provided reasonable assurance of device safety. Animal studies in porcine model included six-month histopathology studies examining local, regional, and systemic effects of Lutonix DCB at 1x and 4x doses, and to evaluate pharmacokinetics. Results demonstrated complete endothelialization, vascular healing, no safety problems, and no systemic effects related to the paclitaxel coating [1]. In addition, paclitaxel levels in porcine arterial tissue at 30 days were sufficient to reduce smooth muscle cell proliferation [2]. Additionally, coating adhesion integrity was assessed during development to assure that the drug is applied uniformly on the balloon during the manufacturing process and does not flake off the balloon during handling in clinical environment. Finally, each batch of finished Lutonix DCB devices undergoes release testing for appearance, identity, potency, content uniformity, impurities, in vitro release, particulate matter and endotoxins to help assure consistent safety and effectiveness for all devices. The Lutonix DCB received CE Mark approval in 2010 and is currently commercialized in over 20 countries.

In collaboration with FDA, Lutonix devised a clinical program to evaluate the safety and efficacy of the Lutonix DCB in the SFA. The first human study of Lutonix DCB for treatment of occlusive femoropopliteal artery disease was Levant 1, a prospective, multicenter, single-blind, randomized (1:1) controlled trial comparing Lutonix DCB to standard (uncoated) balloon angioplasty (PTA). Enrollment of 101 patients was completed in 2009, and 24 month follow-up was completed in 2011. The primary endpoint at 6 months was met, with 58% less late lumen loss for DCB (0.46 vs. 1.09

mm, p = 0.016), 1 year patency was 65.1% in Lutonix DCB compared to 52.5% in PTA in the ITT population, and safety through 24 months was comparable to control PTA[3].

The Levant 2 pivotal IDE trial was a prospective, multicenter, single blind, randomized (2:1) controlled trial comparing Lutonix DCB to standard PTA for treatment of occlusive disease in native femoropopliteal arteries. Unlike prior studies, to investigate the enhancement of paclitaxel on balloon angioplasty without the confounding influence and bias of other therapeutic interventions, Levant 2 was the first femoropopliteal trial to (1) exclude stented patients after predilation prior to randomization, (2) incorporate a very stringent criteria (>50% stenosis and >10mm pressure gradient) for bailout stenting post treatment in both arms, (3) not count stenting as a TLR or failure of any endpoint (4) have a clinician other than the one who performed the index procedure perform 6 and 12 month follow-up clinical evaluations , and (5) blind the clinician performing the 6 and 12 month follow-up assessment to the treatment arm and to the Doppler results. Revascularizations are subject to potential bias when determined by an unblinded investigator; in one prior study reintervention of cases with documented restenosis was 28% for the test vs. 95% for the control group [4]. To ensure thorough understanding of the clinical protocol, the first case at each site was not randomized and was proctored by the sponsor. First patients to receive the Lutonix DCB are referred to as Roll-In subjects and are not included in the primary analysis. Furthermore, to investigate any potential safety effect of paclitaxel, every Adverse Event (AE) and every Serious Adverse Event (SAE) was adjudicated by the CEC. The design of the Levant 2 trial may have set a new bar for femoropopliteal artery studies.

Levant 2 enrollment began in July 2011, and randomization of 476 patients was completed in July 2012. Levant 2 pre-specified two primary endpoints that must both be met in order for the study to be successful. To evaluate whether paclitaxel improved the outcome of angioplasty for the lesion, the primary efficacy endpoint was primary patency at 12 months. Primary patency was defined as freedom from both target lesion restenosis and target lesion revascularization (TLR). Primary patency for Lutonix DCB (65.2%) was superior to control PTA (52.6%, p= 0.015), demonstrating superior efficacy. The primary safety endpoint was freedom from perioperative death and 12 month index limb amputation (above or below the ankle), index limb re-intervention, and index-limb-related death. The primary safety endpoint rate for Lutonix DCB (83.9%) was non-inferior to control PTA (79.0%, p = 0.005) based on an absolute noninferiority margin of 5 percentage points. Sensitivity analyses were conducted to evaluate the influence of missing data on the results; these analyses supported the efficacy and safety conclusions of Levant 2. Point estimates for secondary clinical and patient-reported outcomes generally favored Lutonix DCB. Statistical difference was achieved for the improvement in the walking distance component of WIQ, and a post hoc analysis demonstrated a difference in favour of Lutonix DCB in sustained improvement in Rutherford class without revascularization. Both primary endpoints were met in Levant 2, and superior efficacy and non-inferior safety of Lutonix DCB compared to control PTA was demonstrated.

Furthermore, serious AEs that were adjudicated by the CEC to be probably or highly probably related to the study device and the procedure were comparable for the Lutonix DCB and PTA. A few events (e.g., vascular complications, stroke, CHF, angina, COPD) trended unfavorably for Lutonix DCB in the randomized cohort, and became areas of subsequent investigation in the Levant clinical program. Deaths through 12 months for the Lutonix DCB (n = 7) and the control group (n = 4) were adjudicated as not related to the device, procedure, or index limb. There was a single major amputation (in the DCB group, adjudicated as not device related) and no minor amputations in either group. Freedom from reintervention for treatment of target vessel thrombosis or embolization to its distal vasculature was 99.6% for DCB compared to 99.3% for control PTA. Freedom from procedural embolism was 99.4% for DCB compared to 98.1% for control, consistent with the absence of any increase in embolic risk due to the drug coating.

The Levant 2 Continued Access Safety Registry was initiated upon completion of Levant 2 study. This continued registry followed the same Levant 2 clinical protocol for the test arm in every aspect of inclusion/exclusion criteria, follow-up schedule, and treatment procedure but was not randomized. The study was conducted using the same data collection practices, independent core labs, and CEC adjudication process for SAE's. Per discussion and agreement with FDA, the Levant 2 Continued Access Safety Registry was initiated in 2012 for collection of additional safety data. Enrollment of 657 patients was completed in July 2013. Based on an interim analysis (with follow up of 99% through 30 days, 82% through 6 months, and 35% through 12 months), no new safety risks have been identified, and this complimentary dataset provides additional evidence of the safety profile of Lutonix DCB. Together with the randomized cohort, the Levant 2 studies provide clinical experience from 1029 (including 56 roll-ins, 316 randomized and 657 registry) patients treated with Lutonix DCB who will be followed through 5 years for post-approval analysis.

In conclusion, the results of the Levant 2 Randomized IDE study provide the pivotal clinical evidence supporting the safety and effectiveness of Lutonix DCB and are the basis of this PMA submission, and the other studies in the Levant clinical program are supportive. Levant 2 successfully met both primary (safety and efficacy) endpoints at 12 months by direct comparison to conventional balloon angioplasty. These results demonstrate that treatment of native femoropopliteal lesions with Lutonix DCB provides more durable patency than standard PTA through 12 months with comparable safety and provides a reasonable assurance of safety and effectiveness.

2 BACKGROUND

2.1 Unmet Medical Need in Treatment of Peripheral Artery Disease

Peripheral arterial disease (PAD) is a high cause of patient morbidity. It may present with intermittent claudication resulting in reduced quality of life due to pain in the legs on exercise or with more severe symptoms of critical limb ischemia. The restriction in blood flow that causes the symptoms may be related to disease at a variety of different sites in the legs, including the aortoiliac segments, the femoropopliteal segments, or the smaller infrapopliteal arteries.

PAD is highly prevalent in the general population in the US with an estimated 20% of those over the age of 70 having clinically significant vessel involvement [5]. The femoropopliteal artery, including the superficial femoral artery (SFA) and popliteal artery, is the most commonly involved vessel in the peripheral circulation and the most common site for lower limb interventions [6].

Indications for surgical or endovascular intervention in PAD include claudication, rest pain, and ischemic skin ulceration or gangrene which may progress to ischemic limb loss. Since 1997, a significant change in practice has occurred, with endovascular interventions replacing surgical bypass as the dominant revascularization therapy. The most common intervention is percutaneous transluminal angioplasty (PTA) in which the stenotic artery is dilated with a balloon tipped catheter inserted under fluoroscopic guidance. PTA performed in the femoropopliteal artery is associated with a high one-year restenosis rate, with a recent meta-analysis finding a one-year patency (without surgical or percutaneous reintervention) after PTA of 33% [7].

Patency can be measured invasively using angiography. In every day endovascular clinical practice, however, stenosis in an artery is non-invasively assessed by duplex ultrasonography (DUS). DUS provides a quantitative measure of stenosis, as blood flow in the stenotic region of the artery flows with a higher velocity than in the non-stenotic normal arterial region. Peak systolic velocity ratio (PSVR) is calculated by comparing the DUS flow velocities of a stenotic and a reference region.

Restenosis rates and adverse clinical outcomes are more common in the superficial femoral artery (SFA) because of unique anatomical characteristics that include significant shortening, elongation, torsion, flexion, and vulnerability to external compression [8]. Restenosis is typically caused by neointimal hyperplasia, a hyperproliferative response to the vessel injury that can be caused by angioplasty. As previously stated, angiographic and ultrasound methods have been used to assess restenosis, and the results of one method correlate to the results of the other for binary restenosis, with DUS PSVR $\geq$ 2.5 indicating 50% angiographic stenosis [9-11].

In some lesions, restenosis rates may be reduced when PTA is followed by implantation of bare metal stent (BMS). Recently, self expanding bare nitinol and drug-eluting stents have demonstrated improved patency results, yet restenosis remains a limitation, with 12 month primary patency rates between 63% and 81% [12-16]. However, PTA is still the first line standard-of-care treatment of

femoropopliteal artery disease at many institutions, and it remains the 'class IIa' recommendation of the American College of Cardiology and American Heart Association (ACC/AHA) per the 2011 guideline for management of PAD [17, 18]. Provisional nitinol stent implantation is recommended only in cases where procedural results of angioplasty are not acceptable (e.g. flow-limiting dissection, severe recoil, or >50% residual stenosis with a pressure gradient).

Although stents provide a scaffold to prevent abrupt vessel closure and allow overstretching the vessel beyond its native diameter, they have several disadvantages. Stent outcomes in the femoropopliteal artery are complicated by chronic exposure to the mechanical torsion, flexion, compression, and extension of lower extremity vessels and the possibility of stent fracture [19, 20]. While implantation of BMS or DES can reduce restenosis compared to PTA alone, some regions in the SFA known as "the no stent zone" are not suitable for stenting due to the aforementioned SFA complex anatomical characteristics of high compressions and narrow vessels. Examples are the SFA ostium, adductor hiatus and behind the knee vessels. Implantation of a stent can also cover or 'jail' collaterals and limit the treatment options available to the patient in the event repeat intervention or surgery becomes necessary. In addition, treatment of in-stent restenosis is particularly problematic. Therefore, a significant clinical need remains for a device that is able to achieve more durable patency than PTA but does not require a permanent implant. Lutonix DCB may address this unmet need.

A drug coated balloon (DCB) is a standard angioplasty balloon coated with an antiproliferative agent on the balloon surface. DCB's were approved for use in Europe in 2008. Compared with DES and other existing therapeutic approaches, DCB offers local delivery of an antiproliferative agent to the vasculature without implantation of a stent. In addition to LEVANT 1, three other European randomized pilot studies of paclitaxel-coated DCB's formulated differently by other manufacturers have also demonstrated reduced late lumen loss for DCB with similar safety compared to control PTA when used to treat obstructive femoropopliteal artery disease [4, 21, 22].

DCB has the potential to benefit patients with femoropopliteal artery disease by providing more durable patency than PTA without requiring a permanent implant. This allows a broader population to be treated and preserves flexibility of future therapeutic treatment options for patients with peripheral vascular disease and multiple co-morbidities.

2.2 Proposed Indications For Use

The LUTONIX® 035 Drug Coated Balloon PTA Catheter is indicated for improving luminal diameter for the treatment of obstructive de novo or non-stented restenotic lesions (≤ 15 cm in length) in native femoropopliteal arteries having reference vessel diameters of 4 mm to 6 mm.

2.3 Regulatory and Marketing History

Development of the Lutonix DCB was initiated in 2007 with the first study in patients with femoropopliteal disease (Levant 1) initiated in 2009. CE mark was received in 2010, and the device is commercially available in over 20 countries. In 2012, the post-market Global SFA Registry was initiated that is currently enrolling a heterogeneous population of patients treated with the Lutonix DCB per the commercial IFU.

FDA approved the Levant 2 randomized pivotal IDE study in April 2011, and the trial completed enrollment in July 2012, after which the Levant 2 Continued Access Registry and the Levant 2 Safety Registry were initiated that completed enrollment of 657 patients in September 2013. These two registry protocols are identical to each other and to the randomized protocol, except for randomization; all patients are treated with Lutonix DCB. Inclusion and exclusion criteria, treatment procedure, and follow-up schedule are identical to the Levant 2 randomized protocol. The only difference between the Continued Access and Safety registry studies is that new clinical sites were introduced in the Safety Registry study. For simplicity, the data from the Safety Registry is combined with the data from the Continued Access registry.

The LUTONIX 035 Drug Coated Balloon PTA Catheter has been commercially available outside of the US, including Europe and other countries, for use in treatment of lower limb vascular disease since 2012. To date, one recall has occurred for retrieval of products with weak sterile pouch seal from the pouch supplier; 21 units were identified to be potentially affected which required recall of 165 units in total from the field. This recall was completed on March 2014.

The PMA supporting FDA approval was filed on 25 November 2013 and contains findings from Levant 1 and Levant 2, which were randomized controlled trials conducted to compare safety and efficacy of the Lutonix DCB to control PTA. Interim data from 1029 patients treated with Lutonix DCB in the Levant 2 randomized and registry studies is included in further support of safety and efficacy.

2.4 Device Description

The Lutonix DCB is a combination product comprised of two components: a standard angioplasty balloon catheter providing the primary mode of action (mechanical dilatation of the target lesion) and a drug coating (paclitaxel and excipients polysorbate and sorbitol) to provide an ancillary benefit. The balloon is coated on its outer surface with the drug paclitaxel at a dose density of 2 $\mu g/mm^2$. This results in total paclitaxel amounts ranging from 1.0 mg for the smallest (4 x 40 mm) to 3.8 mg for the largest (6 x 100 mm) balloon size, which are approximately 60-260 times less than the paclitaxel amount in a single infusion of the chemotherapeutic drug Taxol®.

The coating is an immediate release formulation of paclitaxel mixed with the excipients polysorbate and sorbitol to facilitate drug release and tissue deposition. The selection of the coating and the

process used to apply the coating to the balloon was designed to ensure a durable, robust, uniform even coating distribution across the balloon surface and between the two marker bands.

2.4.1 Balloon System

The LUTONIX® 035 Drug Coated Balloon PTA Catheter (LUTONIX® DCB) is an over-the-wire (OTW) percutaneous transluminal angioplasty (PTA) catheter. The LUTONIX® DCB is 0.035" guidewire compatible and has balloon size range from 4.0mm – 6.0mm in diameter and 40mm – 100mm in length. The LUTONIX® DCB is available in 75cm, 100cm and 130cm in working length.

Figure 1: Lutonix 035 DCB PTA Catheter, Model 9004

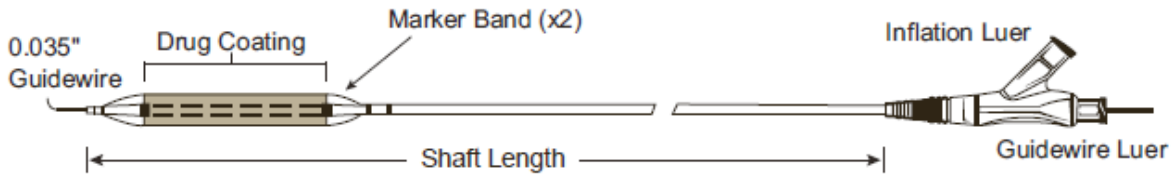


Table 1: Lutonix DCB Balloon Sizes

Balloon Diameters	Balloon Lengths			
	40 mm	60 mm	80 mm	100 mm
4 mm	√	√	√	√
5 mm	√	√	√	√
6 mm	√	√	√	√

2.4.2 Drug Coating

The outer surface of the Lutonix DCB balloon is coated with paclitaxel, a well-known anti-proliferative drug, as the active pharmaceutical ingredient (API) at a dose density of 2 µg/mm2.

Paclitaxel is the same API as used in the FDA approved TAXUS® Express2® Paclitaxel-Eluting Coronary Stent System, TAXUS® Liberté® Paclitaxel-Eluting Coronary Stent System and in the femoropopliteal artery stent Zilver PTX®. Paclitaxel is also the same API in Taxol® (Bristol-Myers Squibb), used for the treatment of certain cancers; the amount of paclitaxel on a Lutonix DCB is is approximately 60-260 times less than the amount used for a single chemotherapeutic dose in treatment with Taxol.

The properties of paclitaxel make it particularly well suited to polymer-free local delivery, avoiding the potential inflammatory and thrombotic reactions that may occur with polymers. Paclitaxel is

highly hydrophobic (i.e., not water soluble), lipophilic, and protein bound. As a result, paclitaxel is readily absorbed into arterial tissue, binding to lipids and proteins within cells and the interstitium.

The mechanism by which the LUTONIX DCB inhibits neointimal growth as seen in preclinical and clinical studies has not been established. Paclitaxel is an antimitotic agent that prevents microtubule deconstruction[23], and paclitaxel inhibits restenosis by preventing migration and proliferation of smooth muscle cells, inflammatory cells, and fibroblasts, and by preventing secretion of extracellular matrix proteins[24]. Paclitaxel is very lipophilic, and it binds tightly to vessel wall tissue and resists wash out into aqueous blood. Paclitaxel has been shown to diffuse transmurally after endoluminal delivery to the vessel wall and to reach concentrations in smooth muscle cell and adventitial cell layers that are 5 to 20-fold higher than at the luminal source[25]. Paclitaxel delivered by LUTONIX DCB has been shown to have a residence time on the order of months in the treated arteries. Animal studies have shown that paclitaxel in the arterial wall reaches a peak level immediately following Lutonix DCB implantation, is sustained near 8% of the peak level at 1 day, at about 1% at 30 days, and is still detectable at 180 days.

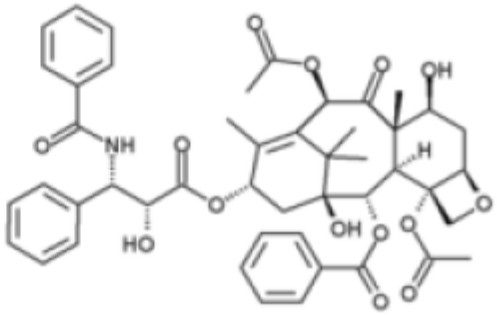
Several studies in animal models have shown that paclitaxel reduces restenosis by inhibiting smooth muscle cell proliferation and neointimal hyperplasia [2, 26]. Clinical studies of the Boston Scientific TAXUS stent and the Cook Zilver PTX stent have demonstrated that paclitaxel reduces restenosis in both the coronary [27] and peripheral femoropopliteal vasculature [16].

The safety profile of paclitaxel has been studied extensively [28]. Systemic administration of paclitaxel in the formulation Taxol at doses appropriate for the treatment of cancer (e.g. solid tumors, ovarian and breast carcinomas) has resulted in hematologic (bone marrow suppression, thrombocytopenia, and anemia), hypersensitivity, cardiovascular (hypotension, bradycardia, no symptomatic ECG) and respiratory side effects. None of these side effects were expected during local delivery with the Lutonix DCB.

Figure 2: Chemical Description of Paclitaxel

Paclitaxel

- Synonyms: Taxol, Taxol A, Hunxol I, Paclitaxelum
- IUPAC systematic name: *β-(benzoylamino)-α-hydroxy-,6,12b-bis(acetyloxy)-12-(benzoyloxy) 2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca(3,4)benz(1,2-b)oxet-9-yl ester,(2aR-(2a-α,4-β,4a-β,6-β,9-α(α-R*,β-S*),11-α,12-α,12a-α,2b-α))-benzenepropanoic acid*
- CAS registry number: 33069-62-4
- Chemical formula: $C_{47}H_{51}NO_{14}$
- Structure of paclitaxel:



Total nominal quantity of paclitaxel on each Lutonix DCB size is shown in Table 2.

Table 2: Paclitaxel Content by Balloon Size

Balloon Diameter (mm)	Total Dosage (mg) per Respective Balloon Length			
	40 mm	60 mm	80 mm	100 mm
4.0	1.0	1.5	2.0	2.5
5.0	1.3	1.9	2.5	3.1
6.0	1.5	2.3	3.0	3.8

Multiple (over 200) formulations were evaluated before proceeding to clinical development with the final formulation. In addition to paclitaxel, the drug coating on Lutonix DCB also contains the excipients polysorbate, a component of FDA-approved products for IV infusion such as pediatric multivitamins, and the endogenous metabolite sorbitol. During balloon inflation, these passive carriers facilitate drug release from the balloon surface and transfer to target artery tissue.

2.4.3 Principles of Operation

As with all angioplasty catheters, the primary action of Lutonix DCB is to dilate an occlusive lesion in a diseased artery. Procedurally, the Lutonix DCB is similar to a standard uncoated PTA catheter with the exception of the following:

- Therapeutic drug delivery occurs during the first inflation of Lutonix DCB. Although additional inflations for mechanical dilatation are allowed, insufficient drug coating remains on the balloon surface for therapeutic effect by subsequent inflations.
- Initial balloon inflation should be a minimum of 30 seconds in duration to allow for therapeutic delivery of the paclitaxel and there is no associated maximum time limit.
- Initial balloon inflation must occur within 3 minutes of insertion into the guide catheter to ensure optimal delivery of the paclitaxel.

3 NON-CLINICAL STUDIES

3.1 Biocompatibility Studies

All materials used in the Lutonix DCB have a long history of clinical use with no reported concerns of toxicity. In addition, a thorough panel of biocompatibility testing was performed on finished, sterilized Lutonix DCBs and delivery systems in accordance with international standard ISO 10993 and 21 CFR 58 Good Laboratory Practice (GLP) requirements and FDA guidance documents on drug eluting stents and PTCA catheters to demonstrate that the components are non-toxic. Additional testing was conducted on both the uncoated PTA catheter and the drug coated balloon component. Details on biocompatibility testing are provided in the draft Summary of Safety and Effectiveness Data (SSED). All results were acceptable and support safety and efficacy of Lutonix DCB for clinical use.

3.2 *In vitro* Bench Testing

Non-clinical *in vitro* bench testing studies were conducted per the FDA Guidance on PTCA catheters in accordance with GLP or according to ASTM standards under pre-determined protocols and controlled conditions. Additional details on bench testing are provided in the draft SSED. In summary, Lutonix DCB meets all the catheter bench testing requirements, including the following:

- Dimensional and Functional Attributes
- Minimum Balloon Burst Strength
- Balloon Compliance
- Balloon Inflation and Deflation Time
- Balloon Fatigue
- Tensile Strength
- Flexibility and Shaft Kink
- Torque Strength
- Balloon Preparation, Delivery and Retrieval
- Radiopacity
- Coating Durability and Particulate Generation
- Coating Uniformity

3.3 Sterilization

The LUTONIX DCB is sterilized using ethylene oxide (EO) sterilization. The cycle is validated per the ISO 11135, and results show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}. In addition, the amount of EtO residual and bacterial endotoxin was verified to be within the specification limits.

3.4 Chemistry, Manufacturing and Controls (CMC) Testing

As part of the CMC testing, and where applicable, the USP and International Conference on Harmonization (ICH) Guidelines were referenced during development of the lot release tests for Lutonix DCB. Each batch of finished devices underwent the CMC release tests shown in Table 3.

Table 3: Chemistry, Manufacturing, and Controls (CMC) Lot Release Testing

Test	Preliminary Acceptance Criteria
Appearance	Visual inspection was conducted to verify that the Lutonix DCB drug coating meets the appearance specification.
Identification	Assays are conducted to verify the identity of the paclitaxel drug on the Lutonix DCB using two different methods.
Assay	Assays are conducted to verify that the total amount of drug on the Lutonix DCB met specification.
Content Uniformity	Multiple catheters are tested for assay content to verify the uniformity of the drug content across the individual catheters.
Related Substances	Assays are conducted to verify the amount and type of degradation products on the Lutonix DCB.
Residual Solvent	The amount of residual solvent is verified to be within the established specification limits.
Dissolution	Dissolution tests are performed to verify that the drug release profile of the Lutonix DCB meets specifications.
Particulate Matter	Simulated use particulate release tests are performed to verify that the simulated use drug release profile of the Lutonix DCB meets specifications.

3.5 Stability/Shelf-Life

Stability studies were conducted to establish a shelf-life/expiration date for the LUTONIX DCB. Functional testing was performed on the aged Lutonix DCB and packaging and analytical testing was performed to confirm the stability of the drug coating.

3.6 Non-clinical *In Vivo* Animal Studies

Preclinical *in vivo* animal studies were conducted to evaluate safety and overall product performance of the Lutonix DCB in porcine arteries for up to six months. Those shown below were conducted in accordance with FDA 21 CFR Part 58 GLP Regulations. Pharmacokinetic studies demonstrated that SFA arterial tissue retains paclitaxel over 30 days post drug delivery. Arterial tissue paclitaxel concentration was 58.8 ± 54.2 ng/mg at 1-hr and 0.3 ± 0.4 ng/mg at 30 days, whereas plasma paclitaxel could no longer be detected after 1 day. The presence of the drug during this time period is important to inhibit smooth muscle cell proliferation and neointimal hyperplasia [29]. The treated arteries displayed minimal endothelial loss, fibrin deposition, and inflammation with long-term drug effect (medial smooth muscle cell loss) peaking at 90 days. In parallel, healing of the treated arteries

was evident by significantly greater medial proteoglycan and collagen deposition at 180 days. To evaluate the safety of the Lutonix DCB formulation, clearance organs (liver, kidneys) and downstream muscular tissues (gastrocnemius, rectus femoris, semimembranosus, and semitendinosus muscles) were evaluated after a treatment with a 4x dose was performed in the SFA porcine model. No evidence of ischemia from downstream emboli or systemic toxicity was observed [1]. The animal studies performed and the acceptable study endpoints supporting product safety and performance are summarized in Table 4.

Table 4: Animal Study Overview

Description / Study #	Animal Model	Devices	Study Design	Time points	Endpoints
Safety Study	22 Domestic Swine	Test – Nominal Dose Lutonix DCB Control- uncoated balloon	Single balloon treatment in Femoral Arteries	28, 90, 180 Days	• Quantitative Angiography • Clinical Safety • Histopathology/SEM • Device handling
Safety Margin Study	23 Domestic Swine	Test – 2x Dose Lutonix DCB Control- uncoated balloon	Two balloons 100% overlapped (4x Dose) in Femoral Arteries	28, 90, 180 Days	• Quantitative Angiography • Clinical Safety • Histopathology/SEM
Pharmacokinetics Study	39 Domestic Swine	Test – Nominal Dose Lutonix DCB	Single balloon treatment in Femoral Arteries	3min, 1hr, 24hr, 7d, 30d, 60d, 90d, & 180d	• Tissue Levels • Organ Levels • Plasma Levels

In summary, the results from animal studies and human clinical data provide a reasonable assurance there is no toxicity due to the paclitaxel drug coating and both support the safety of Lutonix DCB.

4 STUDY INFORMATION

The Levant clinical trial program for the Lutonix DCB includes two randomized, controlled, multicenter clinical studies for treatment of occlusive femoropopliteal artery disease (Levant 1 and Levant 2), and two multicenter, clinical registry studies. The design and current status of clinical studies for which data has been submitted to FDA in support of this PMA for the femoropopliteal indication are summarized in Table 5 and Table 6 below.

Twelve month data from the pivotal Levant 2 randomized study is the basis of this submission, and supplementary interim data from ongoing studies is also provided. Taken together, these studies provide information for over 1400 patients through 30 days, over 1000 patients through 6 months, and over 600 patients through 12-month follow-up after use of Lutonix DCB to treat occlusive femoropopliteal artery disease. A summary of available clinical evidence is provided in the following sections.

Table 5: Design of the Levant Clinical Program – Data Submitted to FDA

	LEVANT 1	**LEVANT 2 Randomized (Pivotal Study)**	**LEVANT 2 Continued Access & LEVANT 2 Safety Registry**	**Lutonix Global SFA Registry**
Study Design				
Study Design	Prospective, multicenter, single blind, randomized 1:1	Prospective, Multicenter, Single Blind, Randomized 2:1	Prospective, Multicenter, Registry	Prospective, Global Multicenter, Single Arm Registry
Control Device	Standard PTA Catheter	Standard PTA Catheter	NA	NA
Sample Size	101 (49 Test DCB & 51 control PTA)	543 476 Randomized (316 DCB & 160 PTA), 56 DCB Roll-In & 11 Std practice	657	Up to 1000
Follow-up	*Clinical:* 1, 6, 12 & 24m *DUS:* 6, 12 & 24m *Angiographic:* 6m	*Clinical*: 6, 12 & 24m *DUS:* 0-30d, 6, 12 & 24m *Telephone:* 1, 36, 48 & 60m	*Clinical*: 6, 12 & 24m *DUS:* 0-30d, 6, 12 & 24m *Telephone:* 1, 36, 48 & 60m	*Telephone or clinical assessment:* 1, 6, 12, & 24m. Patients are consented to 5 years of follow up.

	LEVANT 1	LEVANT 2 Randomized (Pivotal Study)	LEVANT 2 Continued Access & LEVANT 2 Safety Registry	Lutonix Global SFA Registry
Purpose	To assess the safety and efficacy of the Lutonix Catheter for treatment of stenosis of the femoropopliteal arteries by direct comparison to standard balloon angioplasty	To demonstrate the superior efficacy and non-inferior safety of the Lutonix DCB by direct comparison to standard PTA catheter for treatment of stenosis of the femoropopliteal arteries	To assess safety and efficacy of use of the Lutonix DCB for treatment of stenosis of the femoropopliteal arteries in a large population of subjects.	To demonstrate safety and assess the clinical use and outcomes of the Lutonix DCB in a heterogeneous patient population in real world clinical practice.
Primary Endpoint	Angiographic late lumen loss at 6 months	*Efficacy*: Patency of the target lesion at 1 year. *Safety*: Composite of freedom from all-cause peri-operative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb re-intervention, and index-limb-related death.	Rate of unanticipated device- or drug-related adverse events over time through 60 months	*Efficacy*: Freedom from TLR at 12 months. *Safety*: Freedom at 30 days from TVR, major index limb amputation, and device- and procedure-related death.
Enrollment Status	Completed	Completed	Completed	In Process (437 pts enrolled to date)

Table 6: Current Status of Follow-Up by Visit Window for Levant Program

	LEVANT 1		LEVANT 2 Randomized (Pivotal Study)			LEVANT 2 Continued Access & LEVANT 2 Safety Registry	Lutonix Global SFA Registry
Visit	Test DCB n = 49	Control PTA n = 52	Roll-in DCB n = 56	Test DCB n=316	Control PTA n=160	DCB n =657	DCB N= 437
30 days	49 (100%)	48 (92%)	55 (98.2%)	313 (99.1%)	158 (98.8%)	649 (98.8%)	340 (77.8%)
6 months	47 (96%)	45 (87%)	52 (92.9%)	293 (92.7%)	149 (93.1%)	541 (82.3%)	126 (28.8%)
12 months	45 (92%)	41 (79%)	46 (82.1%)	280 (88.6%)	140 (87.5%)	227 (34.6%)	7 (1.6%)
24 months	41 (84%)	38 (73%)	32 (57.1%)	125 (39.6%)	69 (43.1%)	0/0 (0%)	0/0 (0%)

In addition, a randomized clinical study in Japan is ongoing for the femoropopliteal indication along with two FDA IDE randomized controlled studies for SFA in-stent restenosis (ISR) and below-the-knee (BTK) artery disease are underway.

The completed first-in-man clinical trial program was intended to establish biological effect and safety and feasibility of the Lutonix DCB in two vascular beds. Between June and December of 2009, Lutonix enrolled 168 patients in three separate multicenter EU trials in the peripheral and coronary anatomies (Levant 1, PERVIDEO, and De Novo). In the coronary anatomy, PERVIDEO I was a 41-patient single arm in-stent restenosis DCB study and the De Novo Pilot study was a 26-patient single arm DCB plus bare metal stent study. Both studies demonstrated efficacy at 6 months comparable to historic drug eluting stent (DES) outcomes with no unexpected safety events observed through 24 months. Levant 1 randomized 101 patients to Lutonix DCB vs. control PTA for treatment of femoropopliteal lesions. The primary endpoint at 6 months was met, with 58% less late lumen loss for DCB (0.46 vs. 1.09 mm, $p = 0.016$), and safety through 24 months was comparable to control PTA. The first-in-man studies supported the feasibility, safety, and efficacy of the Lutonix DCB for treatment of occlusive artery disease in both the coronary and peripheral vasculature.

Due to the higher unmet clinical need and the feasibility of clinical trial design, clinical development has focused initially on the lower extremity. The pivotal Levant 2 IDE study was designed in collaboration with physicians and with FDA to demonstrate safety and efficacy of the Lutonix DCB for treatment of femoropopliteal lesions.

Table 7: Completed and Ongoing Clinical Studies

Study	Indication	Design	Patients (N)	Geography	Follow-up	Status
PERVIDEO I	CAD ISR	Single arm	41	EU	2 years	Complete
De Novo	CAD De Novo	Single arm	26	EU	2 years	Complete
LEVANT 1	SFA/popliteal	RCT 2:1	101	EU	2 years	Complete
LEVANT 2 Randomized (pivotal IDE)	SFA/popliteal	RCT 2:1	476	US & EU	5 years	1y Primary Endpoint Completed; f/u ongoing
LEVANT 2 Continued Access/Safety Registry	SFA/popliteal	Single arm	650	US & EU	5 years	Enrollment complete; f/u ongoing

Study	Indication	Design	Patients (N)	Geography	Follow-up	Status
LEVANT Japan	SFA/popliteal	RCT 2:1	105	Japan	2 years	Enrolling
Lutonix BTK	BTK (CLI)	RCT 2:1	320	US & EU	5 years	Enrolling
Global SFA Registry	SFA/popliteal	Single arm	Up to 1000	EU	≥ 2 years	Enrolling
Panasia LEG	SFA & BTK	Single arm	Up to 1000	Asia	≥ 2 years	Enrolling
SFA ISR	SFA/pop ISR	RCT 2:1	240	US	5 years	Enrolling
SFA Long Lesions	SFA/pop	Single arm	150	EU	≥ 2 years	Enrolling

As further described below, the results from the Levant 2 randomized study support the safety and effectiveness of Lutonix DCB. Levant 1 and interim results from the single arm studies are provided as supportive information.

5 LEVANT 2 RANDOMIZED IDE CLINICAL STUDY

5.1 Summary of Findings

- Overall, 476 patients met eligibility criteria and were randomized to study treatment at 54 sites (42 in US and 12 in EU), with 316 randomized to Lutonix DCB and 160 to control PTA.
- Demographics, comorbidities, and lesions were well matched between groups.
- The proportion of patients with primary patency at 12 months was 65.2% in the Lutonix DCB group and 52.6% in the control PTA group, meeting the prespecified criteria for superior efficacy ($p = 0.015$) of Lutonix DCB over control PTA.
- The proportion of patients free from composite safety events in the test group was 83.9% compared to 79.0% in the control group at 12 months, and noninferior safety was demonstrated ($p = 0.005$) with an absolute noninferiority margin of 5 percentage points.
- Since both primary endpoints met prespecified criteria for success, the protocol specified hierarchical testing of 12 month target lesion revascularization (TLR), target vessel revascularization (TVR), and superiority of the composite primary safety endpoint. All three endpoints trended in favor of Lutonix DCB but did not reach statistical significance.
- At 12 months, the freedom from TLR rate in the Lutonix DCB group was 87.7% compared to 83.2% in the control group, $p = 0.208$. Unlike prior femoropopliteal PMA studies, bail-out

stenting was not counted as a failure; a post-hoc analysis with procedural stenting counted as a TLR was conducted, and a higher freedom from TLR rate for Lutonix DCB (85.3%) compared to control PTA (76.4%, p = 0.017) was observed at 12 months.

- The ABI values, Rutherford scores, and walking impairment scores each significantly improved (p < 0.001) from before treatment to 12 months in both the Lutonix DCB and PTA groups, with most numerically favoring the DCB group. A significant difference between groups was observed for the walking distance component of the WIQ (DCB-PTA = 9.3; 95% CI [1.6, 17.0]).
- At 12 months, 88.2% of Lutonix DCB patients and 82.4% of PTA patients were clinically improved based on Rutherford Classification. A post-hoc analysis of sustained improvement in Rutherford class without reintervention demonstrates a clinical benefit of Lutonix DCB over control PTA (76.2% vs. 66.6%, p = 0.041).
- Improvement in quality of life (questionnaires EQ-5D and SF-36v2 scores) were similar for both treatment groups.

5.2 Primary Objective

The primary objective of the LEVANT 2 randomized study was to demonstrate the superior efficacy and non-inferior safety of the Lutonix DCB by direct comparison to standard percutaneous balloon angioplasty (PTA) for treatment of stenosis of the femoropopliteal arteries.

5.3 Study Overview

LEVANT 2 was a prospective, controlled, multicenter, multinational, single blind, randomized trial enrolling patients with symptomatic *de novo* or unstented restenotic lesion(s) in the femoropopliteal artery.

Since the primary action of both DCB and PTA is to dilate an obstructive lesion in order to restore flow, the primary efficacy endpoint is primary patency of the treated lesion (i.e., freedom of restenosis and reintervention). Primary patency is assessed noninvasively by DUS since the correlation with angiographic binary restenosis is well established [9-11] and patients are not subjected to an unnecessary invasive procedure. Primary patency as assessed by DUS is the primary endpoint of all modern studies of percutaneous devices for treatment of this indication (e.g. ZILVER PTX, RESILIENT, STROLL, COMPLETE SE, DURABILITY, etc...).

Eligible patients had symptomatic claudication or ischemic rest pain (Rutherford category 2-4) with an angiographically significant atherosclerotic lesion (>70% diameter stenosis) in the superficial femoral and/or popliteal arteries (>1 cm below the common femoral artery bifurcation to >1 cm above the origin of the tibial-peroneal trunk) and a patent outflow artery to the foot. Total target lesion length per patient was <15 cm and reference vessel diameter was 4 to 6 mm.

Patients meeting eligibility criteria underwent protocol defined predilatation before randomization to study treatments. The predilation balloon was a standard PTA balloon inflated to a diameter approximately 1 mm less than the reference vessel diameter (RVD). Following predilatation, patients that were likely to require a stent (major flow-limiting dissection or > 70% residual stenosis) were not randomized in order to minimize the potential for stenting to confound interpretation of the direct comparison between drug coated and uncoated balloons. Patients unlikely to require a stent based on angiographic assessment after predilation were randomized 2:1 to Lutonix DCB or control PTA.

Following randomization, patients were treated with either the Lutonix DCB or control PTA. Investigators selected balloon size based on visual assessment or online QVA and targeted an inflated diameter of 100% of reference vessel diameter (RVD) and length sufficient to treat 5mm proximal and distal to the target lesion and the predilated segment (including overlap of multiple balloons) .

For patients randomized to test DCB, investigators were instructed that although the minimum balloon inflation time for delivery of paclitaxel was 30 seconds, balloons should be inflated for as long as necessary to achieve a satisfactory procedural result, which is the standard of care for all balloon angioplasties. DCB balloon sizes that were included in the study were 4.0-6.0 mm in diameter and 40-100 mm in length. Drug delivery occurs on the first inflation; hence to treat longer lesions, two DCBs must be deployed. An injury segment not completely treated with the Lutonix DCB was defined as “geographic miss”. A minimum overlap of at least 5 mm was required in order to avoid geographic miss and ensure drug delivery to the entire injured segment.

For subjects randomized to the control arm, treatment was performed with uncoated standard PTA catheter(s) per the investigator’s standard angioplasty procedures using a locally approved, off-the-shelf PTA balloon. Use of cutting/scoring balloons was not allowed. The investigator should use an uncoated balloon of similar length and diameter to Lutonix DCB sizes to ensure similarity of treatment between test and control arms. Control balloons may be deflated and repositioned to treat longer lesions, as is common practice for PTA.

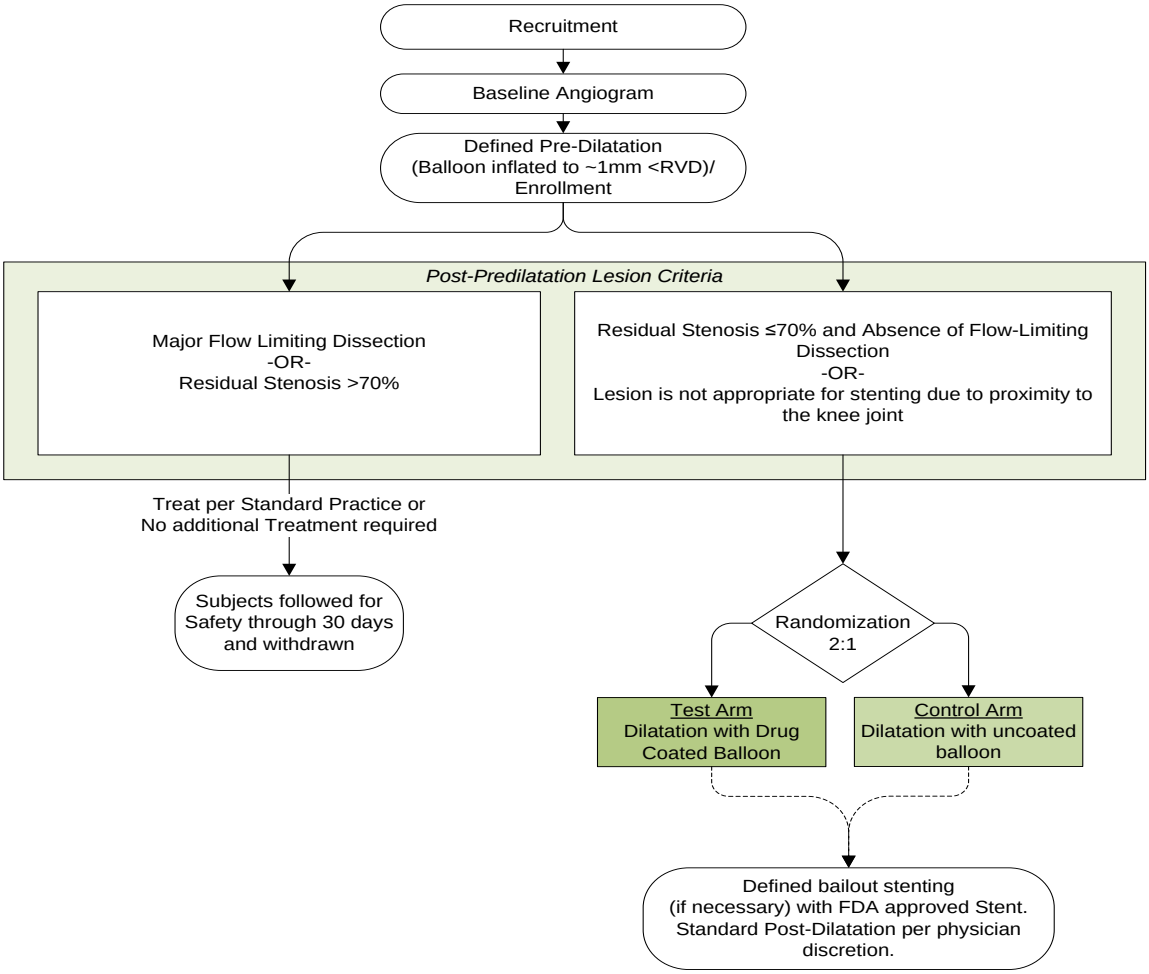
Bailout stenting was allowed in both randomized treatment groups only if the following two criteria were met after treatment and prolonged post-dilatation:

- Residual stenosis >50% (based on in-lab review of angiograms including QVA if available) or major flow-limiting dissection (record angiography in 2 orthogonal views)
- Documented translesional pressure gradient of >20mmHg (using ≤4F end-hole catheter) or >10mmHg (pressure wire) measured immediately distal to the target lesion

Unlike recent femoropopliteal stent PMA studies [15, 16], procedural stenting is not considered a loss of patency or a target lesion revascularization (TLR), and patients with bailout stents are included in the primary analysis.

The procedural flow chart is shown in Figure 3 below.

Figure 3: Procedural Flow Chart



A proctored Lutonix DCB procedure was performed at investigative sites prior to enrolling patients in the randomized portion of the trial. This roll-in patient was intended to train site personnel in proper procedure and data collection. Roll-in patients met all protocol requirements (including inclusion and exclusion criteria) and participated in follow-up, and the sponsor (or designee) was in attendance for training purposes.

Procedural medications were consistent with standard practice. The protocol required dual antiplatelet therapy for a minimum of 1 month, or longer if required by the stent label in case of bail-out stenting.

Patients treated with DCB and standard PTA had in-person clinical visits through two years and will be followed by telephone through five years. As a non-invasive, quantitative diagnostic technique, duplex ultrasound (DUS) was performed during follow up to assess patency of the target lesion and vessel. An initial baseline DUS was performed after the index procedure (up to 1 month ±2 weeks post-procedure), and DUS was required at 6, 12 and 24 month follow-up visits.

5.3.1 Clinical Events Committee (CEC)

All clinical events occurring during the study were adjudicated by the Clinical Events Committee (CEC). The CEC consists of four independent medical experts, blinded to the patients' treatment assignment, including representatives in the field of interventional cardiology, vascular surgery, and interventional radiology with experience in clinical trial safety and adjudication. The CEC consists of an SAE Committee and an Independent Medical Reviewer (IMR). The SAE Committee consists of three physicians who review and adjudicate all serious events and death events. The IMR is a single, independent physician who reviews and assesses all non-serious adverse events. CEC would combine events if reported events actual are all attributed to one event, e.g. site reported chest pain, shortness of breath, elevated cardiac enzymes would be combined to MI. Non events (per CEC Manual) include asymptomatic, untreated, incidental findings, planned procedures to the non target vessel/lesion, normal course of procedure, grade A/B dissections and pre-existing conditions that remain unchanged.

5.3.2 Study Blinding

The patient, DUS technicians, core lab evaluators, and members of the CEC were blinded to treatment assignment. Since the Lutonix DCB looks different than a control PTA device, blinding the interventionalist conducting the index procedure was not feasible. In contrast to historic femoropopliteal studies, Levant 2 is the first to require that both the patient and the investigator conducting the follow-up visit be blinded to treatment assignment until the completion of the 12-month visit. The blinded clinical assessment during follow up was also to be conducted without review of imaging data in order to minimize the potential for introduction of bias into the clinical assessment and decision to reintervene. The Sponsor was blinded until the completion of the 12 month data collection.

5.4 Inclusion and Exclusion Criteria

The inclusion criteria were as follows:

Clinical Criteria

1. Male or non-pregnant female ≥18 years of age;
2. Rutherford Clinical Category 2-4;
3. Subject is willing to provide informed consent, is geographically stable and comply with the required follow up visits, testing schedule and medication regimen;

Angiographic Criteria

Lesion Criteria

4. Length ≤15 cm;

5. Up to two focal lesions or segments within the designated 15 cm length of vessel may be treated (e.g. two discrete segments, separated by several cm, but both falling within a composite length of ≤15 cm);
6. ≥70% stenosis by visual estimate;
7. Lesion location starts ≥1 cm below the common femoral bifurcation and terminates distally ≤2 cm below the tibial plateau AND ≥1 cm above the origin of the TP trunk;
8. *de novo* lesion(s) or non-stented restenotic lesion(s) >90 days from prior angioplasty procedure
9. Lesion is located at least 3 cm from any stent, if target vessel was previously stented;
10. Target vessel diameter between ≥4 and ≤6 mm and able to be treated with available device size matrix;
11. Successful, uncomplicated (without use of a crossing device) antegrade wire crossing of lesion;
12. A patent inflow artery free from significant lesion (≥50% stenosis) as confirmed by angiography (treatment of target lesion acceptable after successful treatment of inflow artery lesions);

NOTE: Successful inflow artery treatment is defined as attainment of residual diameter stenosis ≤30% without death or major vascular complication.

13. At least one patent native outflow artery to the ankle, free from significant (≥50%) stenosis as confirmed by angiography that has not previously been revascularized (treatment of outflow disease is NOT permitted during the index procedure);
14. Contralateral limb lesion(s) cannot be treated within 2 weeks before and/or planned 30 days after the protocol treatment in order to avoid confounding complications;
15. No other prior vascular interventions within 2 weeks before and/or planned 30 days after the protocol treatment.

The exclusion criteria were as follows:

1. Pregnant or planning on becoming pregnant or men intending to father children;
2. Life expectancy of <5 years;
3. Patient is currently participating in an investigational drug or other device study or previously enrolled in this study;

NOTE: Enrollment in another clinical trial during the follow up period is not allowed.

4. History of hemorrhagic stroke within 3 months;
5. Previous or planned surgical or interventional procedure within 2 weeks before or within 30 days after the index procedure;
6. History of MI, thrombolysis or angina within 2 weeks of enrollment;
7. Rutherford Class 0, 1, 5 or 6;
8. Renal failure or chronic kidney disease with MDRD GFR ≤30 ml/min per 1.73 m^2 (or serum creatinine ≥2.5 mg/L within 30 days of index procedure or treated with dialysis);

9. Prior vascular surgery of the index limb, with the exception of remote common femoral patch angioplasty separated by at least 2 cm from the target lesion;
10. Inability to take required study medications or allergy to contrast that cannot be adequately managed with pre- and post-procedure medication;
11. Anticipated use of IIb/IIIa inhibitor prior to randomization;
12. Ipsilateral retrograde access;
13. Composite lesion length is >15 cm or there is no normal proximal arterial segment in which duplex flow velocity can be measured;
14. Significant inflow disease. Successful treatment of inflow disease allowed prior to target lesion treatment;
15. Known inadequate distal outflow (>50% stenosis of distal popliteal and/or all three tibial vessels), or planned future treatment of vascular disease distal to the target lesion;
16. Sudden symptom onset, acute vessel occlusion, or acute or sub-acute thrombus in target vessel;
17. Severe calcification that renders the lesion undilatable;
18. Use of adjunctive primary treatment modalities (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloon, etc.).

5.5 Study Endpoints

5.5.1 Primary Efficacy

The primary efficacy endpoint was primary patency of the target lesion at one year. Primary patency was defined as follows:

- Absence of target lesion restenosis (adjudicated by blinded Doppler core-lab)
- Freedom from target lesion revascularization (TLR) (adjudicated by blinded CEC)

5.5.2 Primary Safety

The primary safety endpoint was a composite of the following:

- Freedom from all cause perioperative (≤ 30 day) death
- Freedom at one year from the following: index limb amputation above or below the ankle, index limb re-intervention, and index-limb-related death (adjudicated by blinded CEC)

5.5.3 Secondary Endpoints

The following secondary efficacy endpoints were evaluated at 6, 12, and 24 months:

- Acute Device, Technical, and Procedural success
- Primary and Secondary Patency
- Alternative Primary and Secondary Patency based on alternative definitions of Duplex Ultrasound (DUS)-derived flow velocities -- PSVR <2.0, <2.5 and <3.0
- DUS Clinical Patency

- Target Lesion Revascularization (TLR)
  - Clinically-driven
  - Total *(clinical and DUS/angiography-driven)*
- Change of Rutherford classification from baseline
- Change of resting Ankle Brachial Index (ABI) from baseline Change in Walking Impairment Questionnaire from baseline
- Change in Six Minute Walk Test from baseline in a subset of patients
- Change in quality of life from baseline, as measured by EQ-5D and SF36-v2 surveys

The following secondary safety endpoints were evaluated:

- Freedom at 30 days from all-cause death, index limb amputation above the ankle and target vessel revascularization (TVR; VIVA Safety Endpoint)
- Composite of freedom from all-cause perioperative (≤30 day) death and freedom from the following at 1, 6, 24, 36, 48, and 60 months: index limb amputation, index limb re-intervention, and index-limb-related death.

The following endpoints were to be assessed at 1, 6, 12, 24, 36, 48 and 60 months:

- All-cause death
- Amputation (above the ankle)-Free Survival (AFS)
- Target Vessel Revascularization (TVR)
- Reintervention for treatment of thrombosis of the target vessel or embolization to its distal vasculature
- Major vascular complications
- Readmission for cardiovascular events

5.6 Statistical Methodology

Statistical analysis of the primary and secondary endpoints was conducted for the pre-specified analysis population including all randomized patients. The primary proportion-based analysis is based on events through the close of the 12 month follow-up window on day 395. Sensitivity analyses are conducted in order to assess the potential impact of missing data, including tipping point, worst case, and Kaplan-Meier probability analyses.

Expected outcomes for sample size calculations were based on 6 month results observed in the LEVANT 1 trial extrapolated to 12 months. The sample size driver of the study was primary efficacy. The assumptions underlying the sample size estimate follow:

- The true 12-month proportion of patients in the Test group with an efficacy event (core-lab adjudicated restenosis and CEC-adjudicated TLR are ‘efficacy events’) is 41%. The true 12-month rate in the Control group is 58%.

- A 2:1 randomization ratio.
- Likelihood ratio chi-square test for inequality of binomial proportions.
- The Type 1 error, $\alpha = 0.05$ (two-sided).
- The Type 2 error, $\beta = 0.10$ (Power = 1 - β = 90%).
- Patients who are censored without having an event will be omitted from the analysis.

Randomization of 476 patients also accounted for an expected 15% loss of patients from the primary analysis due to study exits or missing imaging data as observed in recent femoropopliteal PMA studies of similar populations (of ITT subjects, 17% were non-analyzable in RESILIENT[15], and 21% were missing 12 month DUS in ZILVER PTX[30]).

Primary patency was defined as the absence of core lab adjudicated target lesion binary restenosis at 12 months and freedom from CEC adjudicated target lesion revascularization (TLR) through 12 months. The response variable was failure or success based upon restenosis or TLR in each patient following the index procedure through the close of the 12 month visit window on day 395. All target lesions were evaluated for success or failure, and in case of missing DUS data at 12 months, the following criteria were followed. Patients without analysable DUS at 12 months were included as failures if restenosis was adjudicated on the patient's last evaluable Doppler. Patients without analysable DUS at 12 months were included as successes if absence of restenosis (and freedom from TLR) was adjudicated on a subsequent visit with evaluable DUS.

Sensitivity analyses of primary efficacy results were performed based on alternative peak systolic velocity ratio (PSVR) thresholds for binary restenosis and alternative approaches for inclusion of patients as evaluable versus missing. Worst case and tipping point analyses were also conducted. In the worst-case analysis, an event was assumed to have occurred at the time the patient discontinued participation in the study for all such patients in the test group, while in the control group, all patients with missing data were assumed not to have had an event. In the tipping-point analysis, assumptions about missing data are varied from worst-case to best-case to examine at what point the missing data would alter the results of the analysis.

The primary safety endpoint was defined as the composite of freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following "safety events": index limb amputation (above or below the ankle), index limb re-intervention, and index-limb-related death. This endpoint includes assessment of clinically significant systemic and downstream vascular complications at 1 year by assessing freedom from all-cause index limb re-intervention (e.g., PTA or surgical bypass) for any reason (e.g. embolism, thrombosis, or restenosis), all index limb amputations (including both major and minor amputations below-the ankle), index-limb-related death, and all-cause perioperative (≤30 day) death.

The randomized sample size of 476 patients required for efficacy endpoint testing was expected to provide >95% power for the primary safety test, based on outcomes observed at 6 months in the LEVANT 1 trial carried forward to 12 months. The statistical analysis for primary safety was a one-sided Farrington & Manning test for non-inferiority of proportions at α=0.025. The non-inferiority margin was set at 5 points on a percentage scale. The response variable in each patient was the presence or absence of at least one safety event from the time following the index procedure through 12 months. Each component of the composite was assessed through the upper end of the 12 month window in order to account for intervention/action that resulted from findings at the 12 month visit. Patients with follow-up visits (outside the window) are included in the analysis only if the in-window endpoint result may be conclusively inferred from data obtained later. Patients known to have not had a safety event through 395 days but who had a later event are considered successes at 12 months. Patients who did not have a visit within or after the 12 month follow-up window or exited prior to the 12 month visit were excluded from the primary analysis if they did not have a prior safety event and the in-window result was not demonstrated by information obtained later. Patients who had a safety event prior to exiting the study or prior to the expected 12 month visit were considered failures.

In order to maintain an overall alpha level of 0.05, the following secondary endpoints were to be tested in order if and only if both primary endpoint evaluations were successful: TLR at 12 months, TVR at 12 months, and composite safety (for superiority) at 12 months. Each endpoint would be tested and only if declared successful would the next endpoint be tested.

5.7 Subject Disposition

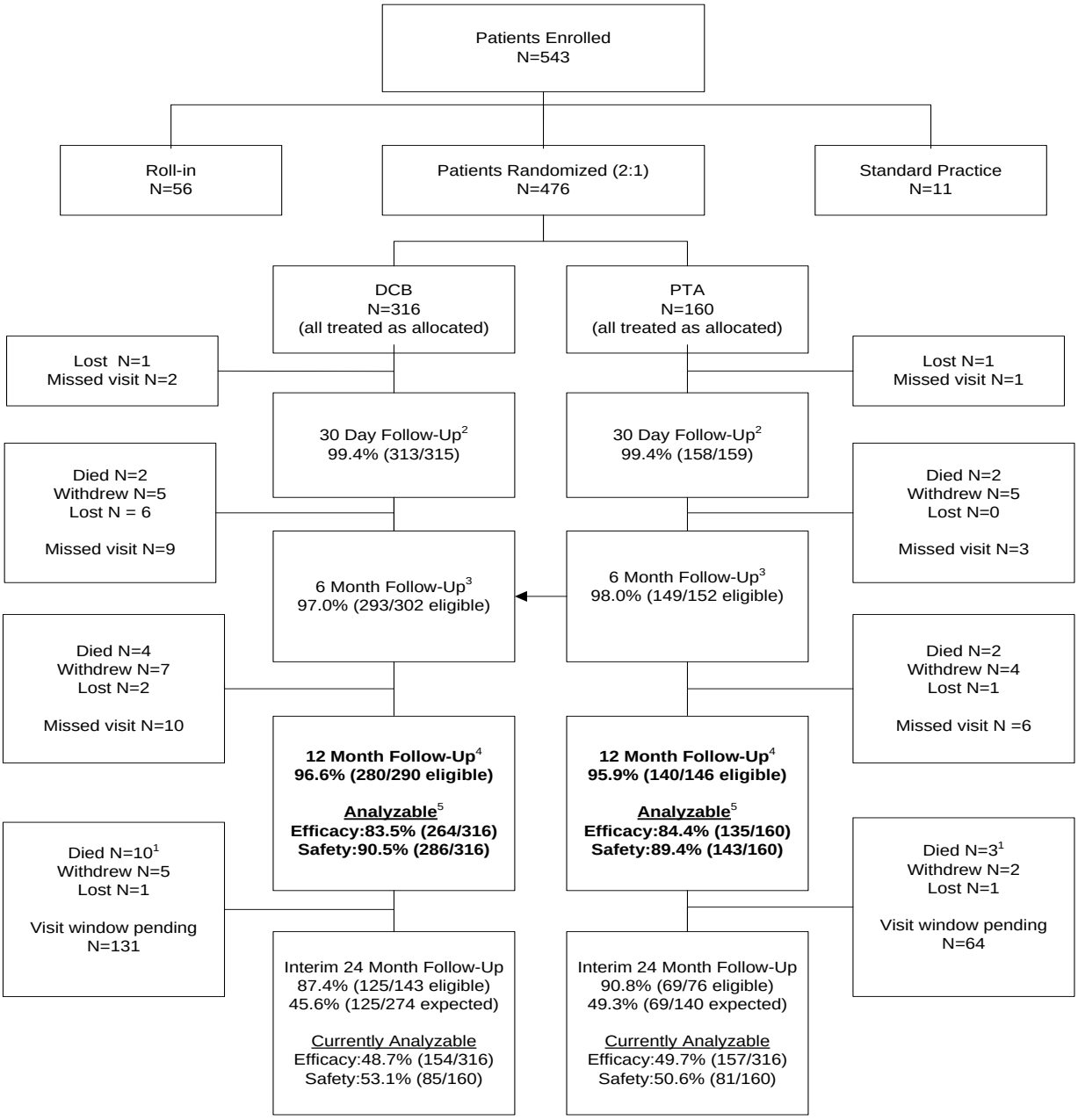
Five hundred forty-three (543) patients were enrolled in this study, of which 476 patients were randomized 2:1 to Lutonix DCB (n=316) and PTA (n=160). Not included in the primary analysis are 56 roll-in patients treated with Lutonix DCB (including 3 live cases) and 11 subjects treated per standard practice that were not randomized.

Participant flow through the trial is displayed in Figure 4, including treatment allocation, disposition, follow-up compliance, and whether analyzable for primary endpoint evaluation. Overall, 96.3% (420/436) of patients who had not previously exited the study (88.2% on an ITT basis of 476 randomized subjects) completed 12 month follow up. Reasons for premature discontinuation were similar between treatment groups, with withdrawal of consent being most common. On an ITT basis, 88.6% (280/316) of subjects in the Lutonix DCB arm and 87.5% (140/160) of subjects in the PTA arm completed their 12-month evaluation.

Follow-up compliance in LEVANT 2 compares favorably with recent femoropopliteal PMA studies. In RESILIENT, 12-month follow-up was available for 87.2% of eligible (non-exited) patients and 83.0% of randomized ITT patients [15]. The Zilver PTX analysis differed from that of RESILIENT and LEVANT 2 in that a submitted death form, withdrawal form, or loss to follow-up form were counted as followed-up (while these were counted as missing in RESILIENT and LEVANT 2)[30].

LEVANT 2 follow-up is ongoing, and 46.9% (194/414) of non-exited subjects had completed 24 month follow-up as of the February 26, 2014 database export.

Figure 4: LEVANT 2 Consort Flow Diagram



[1] One DCB subject died within the 12-month follow-up window after a 12-month follow-visit and is shown as exiting between 12 and 24 months. Deaths beteween 12 and 24 months include (n =6 DCB vs 2 PTA) that have not yet been CEC adjudicated. Exit reason "other" (n=2 vs 1) are included as lost.

[2] Only telephone contact was required per protocol at 30 days; 158 (50.3%) DCB vs. 79 (49.7%) of patients had in-person clinical visits.

[3] At 6 months, clinical information was obtained by telephone for n= 6 vs. 3 patients, and 287 (95.0%) DCB vs. 146 (96.1%) PTA patients had in-person clinical visits.
[4] At 12 months, clinical information was obtained by telephone for n =11 vs 5 patients, and 269 (93.7%) DCB vs 135 (93.1%) PTA had in-person clinical visits.
[5] All endpoint failures occurring prior to study discontinuation are included as Analyzable ITT. Analysis for Primary Safety requires evaluable clinical follow-up only; Primary Efficacy requires both evaluable Doppler and evaluable clinical follow-up.

5.8 Demographics and Baseline Characteristics

Demographic characteristics were generally well balanced by treatment group (Table 8). Across both groups, the mean age was 68.2 and there were more males (63%) than females (37%). The overall BMI was about 29.

Table 8:Summary of Demographic Characteristics by Treatment group in LEVANT 2

Variable	Lutonix DCB	Control PTA	P-value[1]	Pooled
Age (years), Mean ± SD (n) median (min, max)	67.8 ± 10.0 (316) 68.2 (44.5, 91.4)	69.0 ± 9.0 (160) 69.0 (41.5, 89.4)	0.207	68.2 ± 9.7 (476) 68.4 (41.5, 91.4)
Gender, % (n/N)			0.216	
Female	38.9% (123/316)	33.1% (53/160)		37.0% (176/476)
Male	61.1% (193/316)	66.9% (107/160)		63.0% (300/476)
Ethnicity, % (n/N)			0.741	
Hispanic or Latino	7.9% (25/316)	8.8% (14/160)		8.2% (39/476)
Not Hispanic or Latino	91.8% (290/316)	91.3% (146/160)		91.6% (436/476)
Patient chose not to respond	0.3% (1/316)	0.0% (0/160)		0.2% (1/476)
Race, % (n/N)			0.160	
Asian	1.3% (4/316)	2.5% (4/160)		1.7% (8/476)
Black or African American	3.8% (12/316)	8.1% (13/160)		5.3% (25/476)
Patient chose not to respond	4.1% (13/316)	4.4% (7/160)		4.2% (20/476)
White	90.8% (287/316)	85.0% (136/160)		88.9% (423/476)
Height (cm), Mean ± SD (n) median (min, max)	169.3 ± 10.3 (316) 170.0 (135.0, 194.0)	170.3 ± 10.1 (160) 171.5 (142.0, 190.0)	0.335	169.6 ± 10.2 (476) 170.0 (135.0, 194.0)
Weight (kg), Mean ± SD (n) median (min, max)	83.1 ± 17.0 (316) 82.0 (42.0, 146.0)	82.5 ± 17.1 (160) 80.0 (48.0, 133.0)	0.709	82.9 ± 17.0 (476) 82.0 (42.0, 146.0)
BMI (kg/m^2), Mean ± SD (n) median (min, max)	29.0 ± 5.3 (316) 28.5 (15.8, 52.7)	28.3 ± 4.8 (160) 27.9 (18.1, 48.5)	0.221	28.7 ± 5.2 (476) 28.1 (15.8, 52.7)

[1] T-tests for means and X^2-tests for proportions

Baseline medical characteristics were also generally well balanced by treatment group (Table 9). The most common comorbidities include dislipidemia, hypertension, previous coronary artery disease, obesity, and smoking. There was a similar frequency of diabetes treated in both groups, although a higher percentage of these were Type I for the test arm. There was a similar frequency of prior stroke, although a lower percentage of these were ischemic in the test arm. Overall, comorbidities at baseline were well-matched and representative of the patient population with peripheral vascular disease [31].

Most patients in each treatment group were taking cardiac medications at baseline with 87.3% and 93.8% of the Lutonix DCB and control PTA groups taking aspirin, 77.2% and 78.8% taking statins, 51.3% and 43.1% taking clopidogrel, 57.3% and 56.3% taking beta blockers, and 46.8% and 45.0% taking ACE inhibitors.

The majority of patients in each treatment group were Rutherford grade 3 (Table 9), and 8% had critical limb ischemia (Rutherford Class 4). ABIs in target and contralateral limbs were also similar by treatment group.

Table 9: Baseline Medical Characteristics in LEVANT 2

Variable	Lutonix DCB	Control PTA	P-value[1]	Pooled
BMI>=30, % (n/N)	34.8% (110/316)	30.6% (49/160)	0.360	33.4% (159/476)
Smoking, % (n/N)			0.548	
Current smoker	35.1% (111/316)	33.8% (54/160)		34.7% (165/476)
Never smoked	20.9% (66/316)	17.5% (28/160)		19.7% (94/476)
Previously smoked	44.0% (139/316)	48.8% (78/160)		45.6% (217/476)
Dyslipidemia/Hypercholesterolemia % (n/N)	89.6% (283/316)	86.3% (138/160)	0.286	88.4% (421/476)
Diabetes Mellitus, % (n/N)	43.4% (137/316)	41.9% (67/160)	0.758	42.9% (204/476)
Type			0.034	
Type I	9.5% (13/137)	1.5% (1/67)		6.9% (14/204)
Type II	90.5% (124/137)	98.5% (66/67)		93.1% (190/204)
Insulin Dependency	40.9% (56/137)	40.3% (27/67)	0.937	40.7% (83/204)
Hypertension, % (n/N)	89.2% (282/316)	87.5% (140/160)	0.572	88.7% (422/476)
Renal Failure, % (n/N)	3.5% (11/316)	4.4% (7/160)	0.629	3.8% (18/476)
Congestive Heart Failure, % (n/N)	5.7% (18/316)	3.1% (5/160)	0.217	4.8% (23/476)
Previous CAD, % (n/N)	49.7% (157/316)	48.1% (77/160)	0.748	49.2% (234/476)
Previous MI, % (n/N)	19.9% (63/316)	17.5% (28/160)	0.523	19.1% (91/476)

Variable	Lutonix DCB	Control PTA	P-value[1]	Pooled
Chronic Angina, % (n/N)	4.7% (15/316)	5.0% (8/160)	0.903	4.8% (23/476)
History of Coronary Revascularization, % (n/N)	41.8% (132/316)	38.8% (62/160)	0.526	40.8% (194/476)
Type of Coronary Revascularization			0.429	
CABG	45.2% (47/104)	52.1% (25/48)		47.4% (72/152)
PCI	54.8% (57/104)	47.9% (23/48)		52.6% (80/152)
Previous Cerebrovascular Event, % (n/N)	11.4% (36/316)	11.3% (18/160)	0.963	11.3% (54/476)
Ischemic	75.0% (27/36)	100.0% (18/18)		83.3% (45/54)
Hemorrhagic	5.6% (2/36)	0.0% (0/18)		3.7% (2/54)
Previous Target Limb Intervention, % (n/N)	23.4% (74/316)	17.5% (28/160)	0.137	21.4% (102/476)
Target Vessel Type			0.292	
DeNovo Target Vessel	83.9% (265/316)	87.5% (140/160)		85.1% (405/476)
Restenosed Target Vessel	16.1% (51/316)	12.5% (20/160)		14.9% (71/476)

[1] T-tests for means and X^2-tests for proportions

Table 10: Rutherford Grade and ABI of Target Limb

Variable	Lutonix DCB	Control PTA	P-value[1]	Pooled
Rutherford Grade, % (n/N)			0.521	
2	29.4% (93/316)	34.4% (55/160)		31.1% (148/476)
3	62.7% (198/316)	57.5% (92/160)		60.9% (290/476)
4	7.9% (25/316)	8.1% (13/160)		8.0% (38/476)
ABI of Target Limb[2], Mean ± SD (n) median (min, max)	0.74 ± 0.20 (306) 0.73 (0.00, 1.38)	0.73 ± 0.18 (156) 0.73 (0.00, 1.17)	0.467	0.74 ± 0.20 (462) 0.73 (0.00, 1.38)
ABI of Contralateral, Mean ± SD (n) median (min, max)	0.87 ± 0.23 (301) 0.92 (0.00, 1.34)	0.87 ± 0.20 (152) 0.89 (0.00, 1.30)	0.783	0.87 ± 0.22 (453) 0.91 (0.00, 1.34)

1 T-tests for means and X2-tests for proportions

[2] Pressures > 1.4 were excluded from this analysis (n = 3 for Lutonix DCB, n = 1 for PTA) per the Measurement and Interpretation of the Ankle-Brachial Index guidelines from the American Heart Association

5.8.1 Lesion Characteristics

Treatment groups were well-balanced with respect to number of lesions treated, lesion length, diameter of stenosis, lesion class, percent occlusion, lesion location, and run-off vessels (Table 11). Lesion length was 62.8 ± 41.0 mm. Approximately 59% of lesions were calcified (9.7% severely so) and 21% were totally occluded.

Table 11: Characteristics of Treated Lesions

Variable[1]	Test DCB	Control PTA	P-value[2]	Pooled
Number of Lesions Treated, % (n/N)			0.400	
1	98.1% (310/316)	96.9% (155/160)		97.7% (465/476)
2	1.9% (6/316)	3.1% (5/160)		2.3% (11/476)
Total Target Lesion Length (mm, core lab), Mean ± SD (n) median (min, max)	62.7 ± 41.4 (315) 51.5 (5.7, 196.7)	63.2 ± 40.4 (160) 51.8 (7.5, 173.7)	0.900	62.8 ± 41.0 (475) 51.6 (5.7, 196.7)
Total Target Lesion Length (mm, site), Mean ± SD (n) median (min, max)	69.6 ± 43.8 (316) 70.0 (1.0, 150.0)	69.6 ± 43.9 (160) 70.0 (2.0, 150.0)	0.987	69.6 ± 43.8 (476) 70.0 (1.0, 150.0)
Treated Length (mm), Mean ± SD (n) median (min, max)	107.9 ± 47.0 (316) 105.3 (29.9, 233.9)	107.9 ± 49.4 (160) 103.4 (23.3, 307.7)	0.988	107.9 ± 47.8 (476) 104.9 (23.3, 307.7)
Maximum Percent Stenosis, %DS, Mean ± SD (n) median (min, max)	80.5 ± 14.8 (316) 81.0 (40.0, 100.0)	80.9 ± 14.9 (160) 82.0 (45.0, 100.0)	0.776	80.6 ± 14.8 (476) 81.0 (40.0, 100.0)
Average RVD (mm), Mean ± SD (n) median (min, max)	4.8 ± 0.8 (316) 4.7 (3.0, 7.5)	4.8 ± 0.8 (160) 4.7 (2.8, 7.1)	0.981	4.8 ± 0.8 (316) 4.7 (3.0, 7.5)
Target Limb, % (n/N)			0.841	
Left	52.8% (167/316)	51.9% (83/160)		52.5% (250/476)
Right	47.2% (149/316)	48.1% (77/160)		47.5% (226/476)
Lesion Class TASC II, % (n/N)			0.398	
A	76.3% (241/316)	75.6% (121/160)		76.1% (362/476)
B	21.5% (68/316)	23.8% (38/160)		22.3% (106/476)
C	2.2% (7/316)	0.6% (1/160)		1.7% (8/476)
Calcification, % (n/N)	59.2% (187/316)	58.1% (93/160)	0.826	58.8% (280/476)

Variable[1]	Test DCB	Control PTA	P-value[2]	Pooled
Severe Calcification	10.4% (33/316)	8.1% (13/160)	0.419	9.7% (46/476)
Total Occlusion, % (n/N)	20.6% (65/316)	21.9% (35/160)	0.741	21.0% (100/476)
Number of Patent Run-Off Vessels, Mean ± SD (n) median (min, max)	2.1 ± 1.0 (316) 2.0 (0.0, 3.0)	1.9 ± 1.0 (160) 2.0 (0.0, 3.0)	0.148	2.0 ± 1.0 (476) 2.0 (0.0, 3.0)
Number of Patent Run-Off Vessels (Categorical), % (n/N)			0.539	
0	9.5% (30/316)	13.1% (21/160)		11.1% (53/476)
1	15.2% (48/316)	16.9% (27/160)		15.8% (75/476)
2	35.4% (112/316)	35.0% (56/160)		34.9% (166/476)
3	39.9% (126/316)	35.0% (56/160)		38.2% (182/476)
Most Distal Lesion Location, % (n/N)			0.495	
Proximal SFA	9.2% (29/316)	8.1% (13/160)		8.8% (42/476)
Mid SFA	51.3% (162/316)	45.6% (73/160)		49.4% (235/476)
Distal SFA	29.7% (94/316)	38.8% (62/160)		32.8% (156/476)
Proximal Popliteal	4.7% (15/316)	4.4% (7/160)		4.6% (22/476)
Mid Popliteal	4.1% (13/316)	2.5% (4/160)		3.6% (17/476)
Distal Popliteal	0.9% (3/316)	0.6% (1/160)		0.8% (4/476)
Most Distal Lesion Location Rank[3], Mean ± SD (n) median (min, max)	2.46 ± 0.94 (316) 2.00 (1.00, 6.00)	2.49 ± 0.85 (160) 2.00 (1.00, 6.00)	0.721	2.47 ± 0.91 (476) 2.00 (1.00, 6.00)

[1] All values per angiographic core lab except where indicated
[2] T-tests for means and X2-tests for proportions
[3] Lesion locations are ranked 1-6 from least to most distal, in the order displayed.

5.8.2 Procedural Characteristics

Table 12 summarizes the procedural data by treatment group. Significantly more balloons were used in the Lutonix DCB group than in the control PTA group (mean of 1.37 compared to a mean of 1.13 balloons, respectively; $p < 0.001$). This difference is most likely due to the fact that a new Lutonix DCB balloon must only be used once to treat different or overlapping lesions (to deliver drug). In contrast, control PTA balloons can be repositioned and reinflated.

The mean inflation time of in the Lutonix DCB group (151.2 seconds) was significantly less than in the control PTA control group (173.6 seconds, $p = 0.004$). Literature has shown that longer inflation times can lead to improved outcomes with balloon angioplasty group [32]. It is reasonable to speculate that the longer inflation time for the control PTA would likely benefit the outcomes for the

control PTA arm over the Lutonix DCB group. Another procedural difference between the two groups is the inflation pressure. Inflation pressure was less in Lutonix DCB (7.8 vs. 8.4 atm, p = 0.002). Inflation pressure is determined by the compliance curves at which a balloon reaches its optimal diameter. It depends on the design, material, and size of the balloon and is manufacturer specific. Therefore, this difference is less relevant since the desired outcome is optimal inflation for the appropriate balloon.

The site-reported dissection rate after treatment was similar between treatment groups (39.6% vs. 38.8%, p = 0.865), as were treated dissections (36.0% vs. 37.1%, p = 0.883). However, core lab adjudicated Grade C or higher dissections were observed less frequently after treatment with test DCB than control PTA devices (2.5% vs. 7.5%, p = 0.034), consistent with the lower observed frequency of bailout stenting (2.5% vs. 6.9%, p = 0.022). Geographic miss was adjudicated by the blinded core lab less frequently in the test than in the control group (7.6% vs. 21.9%, p < 0.001), this difference will be discussed in further detail in 5.9.3.

Final procedural results were similar for both test and control groups respectively, with 88.9% vs. 86.8% procedural success and 20.9% vs. 21.0% residual diameter stenosis.

Table 12: Procedural Data by Treatment Group

Variable	Lutonix DCB	Control PTA	P-value[2]	Pooled
Contralateral Access, % (n/N)	73.4% (232/316)	73.8% (118/160)	0.938	73.5% (350/476)
Inflow Tract Stenosis Treated, % (n/N)	0.9% (3/316)	1.9% (3/160)	0.392	1.3% (6/476)
Predilation				
Predilation Performed (All Lesions), % (n/N)	100.0% (316/316)	100.0% (160/160)		100.0% (476/476)
Predilation Overstretch (Inflated Diamteter/RVD, core lab), Mean ± SD (n) median (min, max)	0.8 ± 0.2 (283) 0.8 (0.3, 1.3)	0.8 ± 0.2 (138) 0.8 (0.5, 1.3)	0.234	0.8 ± 0.2 (421) 0.8 (0.3, 1.3)
Maximum %DS Post Predilation (Core Lab), Mean ± SD (n) median (min, max)	40.8 ± 12.9 (312) 41.0 (2.0, 88.0)	41.9 ± 13.5 (156) 41.0 (12.0, 80.0)	0.375	41.1 ± 13.1 (468) 41.0 (2.0, 88.0)
As-randomized study device treatment				
Total Number of Treatment Balloons, Mean ± SD (n) median (min, max)	1.37 ± 0.50 (316) 1.00 (1.00, 3.00)	1.13 ± 0.35 (160) 1.00 (1.00, 3.00)	<0.001	1.29 ± 0.47 (476) 1.00 (1.00, 3.00)
Total Number of Treatment Balloons (Categorical), % (n/N)			<0.001	
1	63.9% (202/316)	88.1% (141/160)		72.1% (343/476)
2	35.4% (112/316)	11.3% (18/160)		27.3% (130/476)
3	0.6% (2/316)	0.6% (1/160)		0.6% (3/476)
Total Paclitaxel on Balloons Used per patient (mg), Mean ± SD (n) median (min, max)	3.5 ± 1.8 (316) 3.1 (1.0, 11.3)	N/A		3.5 ± 1.8 (316) 3.1 (1.0, 11.3)
Transit Time per Balloon (seconds), Mean ± SD (n) median (min, max)	35.2 ± 27.2 (432) 30.0 (3.0, 179.0)	N/A		35.2 ± 27.2 (432) 30.0 (3.0, 179.0)
Inflation Time per Balloon (seconds), Mean ± SD (n) median (min, max)	151.2 ± 78.1 (432) 120.0 (30.0, 480.0)	173.6 ± 109.6 (180) 135.0 (10.0, 630.0)	0.004	157.8 ± 89.0 (612) 120.0 (10.0, 630.0)

Variable	Lutonix DCB	Control PTA	P-value[2]	Pooled
Maximum Pressure of Study Balloons (per balloon), Mean ± SD (n) median (min, max)	7.8 ± 2.0 (432) 8.0 (4.0, 14.0)	8.4 ± 2.6 (180) 8.0 (3.0, 14.0)	0.002	8.0 ± 2.2 (612) 8.0 (3.0, 14.0)
Treatment Overstretch (inflated diameter/RVD), Mean ± SD (n) median (min, max)	0.9 ± 0.2 (293) 0.9 (0.5, 1.6)	1.0 ± 0.2 (146) 1.0 (0.6, 1.7)	0.087	0.9 ± 0.2 (439) 0.9 (0.5, 1.7)
Dissection post-study treatment (Core Lab), % (n/N)	63.4% (199/314)	71.7% (114/159)	0.071	66.2% (313/473)
Dissection Grade post-study treatment (Core Lab)			0.034	
Grade A	37.6% (118/314)	38.4% (61/159)		37.8% (179/473)
Grade B	23.2% (73/314)	25.8% (41/159)		24.1% (114/473)
Grade C	2.5% (8/314)	7.5% (12/159)		4.2% (20/473)
Dissection post-study treatment (Site Reported), % (n/N)	39.6% (125/316)	38.8% (62/160)	0.865	39.3% (187/476)
Maximum %DS Post study treatment (Core Lab, All Lesions), Mean ± SD (n) median (min, max)	23.4 ± 12.3 (316) 24.0 (0.0, 100.0)	23.8 ± 12.3 (158) 24.0 (0.0, 59.0)	0.703	23.5 ± 12.3 (474) 24.0 (0.0, 100.0)
Additional Treatments (Any Lesion)				
PTA, % (n/N)	21.5% (68/316)	20.0% (32/160)	0.701	21.0% (100/476)
Stent, % (n/N)	2.5% (8/316)	6.9% (11/160)	0.022	4.0% (19/476)
Final Procedural Outcome				
Maximum %DS Post Procedure (Core Lab, All Lesions), Mean ± SD (n) median (min, max)	20.9 ± 9.8 (316) 22.0 (0.0, 47.0)	21.0 ± 10.2 (159) 22.0 (0.0, 47.0)	0.914	20.9 ± 9.9 (475) 22.0 (0.0, 47.0)
Minimum Lumen Diameter (MLD) Post procedure (Core Lab, All Lesions), Mean ± SD (n) median (min, max)	3.8 ± 0.7 (316) 3.8 (2.4, 6.0)	3.9 ± 0.7 (159) 3.8 (2.4, 6.4)	0.365	3.8 ± 0.7 (475) 3.8 (2.4, 6.4)
Procedure Duration (Minutes), Mean ± SD (n) median (min, max)	57.6 ± 29.8 (316) 54.0 (14.0, 268.0)	56.6 ± 29.2 (160) 52.0 (8.0, 161.0)	0.741	57.3 ± 29.6 (476) 53.5 (8.0, 268.0)

Variable	Lutonix DCB	Control PTA	P-value[2]	Pooled
Geographic Miss1 (Any Lesion), % (n/N)	7.6% (24/316)	21.9% (35/160)	<0.001	12.4% (59/476)
Procedural Embolism, % (n/N)	0.6% (2/316)	1.9% (3/160)	0.209	1.1% (5/476)
Procedural Success (Core Lab, All Lesions), % (n/N)	88.9% (281/316)	86.8% (138/159)	0.497	88.2% (419/475)

[1] Core lab adjudication if known, otherwise site adjudication.
[2] T-tests for means and X^2-tests for proportions.

5.9 Primary Endpoints: Primary Patency and Composite Safety

5.9.1 Primary Patency

Primary patency is defined as the absence of restenosis (as adjudicated by the blinded core-lab) and freedom from Target Lesion Revascularization (as adjudicated by the CEC). Overall, 83.5% (264/316) test DCB subjects and 84.4% (135/160) control PTA subjects were evaluable for primary efficacy endpoint testing at 12 months. The percentage of ITT subjects with analyzable patency in LEVANT 2 is comparable to recent PMA trials for this indication (e.g., 83% analyzable in RESILIENT). Section 5.9.1.1 provides a summary of the reasons for exclusion and findings from sensitivity analyses to address the impact of missing data on the analysis.

The proportion of subjects with primary patency at 12 months was 65.2% in the Lutonix DCB group and 52.6% in the control PTA group, and superior efficacy (p = 0.015) of Lutonix DCB over control PTA was demonstrated (Table 13).

Table 13: Primary Efficacy Endpoint – Primary Patency at 1 Year (ITT Population)

Measure	Lutonix DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
Primary Patency[1]	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.015

[1]Primary Patency is defined freedom from target lesion restenosis (defined by DUS core lab adjudication) and target lesion revascularization (TLR).
[2]Based on asymptotic likelihood ratio test. CIs for groups and difference are asymptotic.

Efficacy events are shown in Table 14 below. Both components favor Lutonix DCB, with about one-third of the difference in primary efficacy driven by the nominal difference in TLR. The percentage of patency failures leading to target lesion revascularization (TLR) was similar for Lutonix DCB (38.0% (35/92)) and control PTA (37.5% (24/64)), consistent with absence of reintervention bias in clinical assessments blinded to treatment group and DUS imaging results.

Table 14: Efficacy Events through 1 Year

Efficacy Event	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]
TLR*	13.3% (35/264) [9.2, 17.3]	17.8% (24/135) [11.3, 24.2]	-4.5% [-12.2, 3.1]
Adjudicated Restenosis without TLR	21.6% (57/264) [16.6, 26.6]	29.6% (40/135) [21.9, 37.3]	-8.0% [-17.2, 1.1]

*Target vessel surgical bypass (2 vs. 1) included as TLR.

The primary efficacy endpoint findings are preserved after adjusting for covariates (unadjusted Odds Ratio (OR) = 0.59, p = 0.015 vs. adjusted OR = 0.57, p = 0.015).

5.9.1.1 Sensitivity Analyses of Primary Patency

Table 15 provides a summary of patients who were and were not analyzable. Overall, 16.5% (52/316) of patients randomized to Lutonix DCB and 15.6% (25/160) of patients randomized to control PTA were excluded from analysis of primary patency. Reasons for exclusion were similar for both treatment groups; the most common causes were missing diagnostic DUS at 12 months (6.0% vs. 5.6%) and prior withdrawal of consent (4.1% vs. 5.6%).

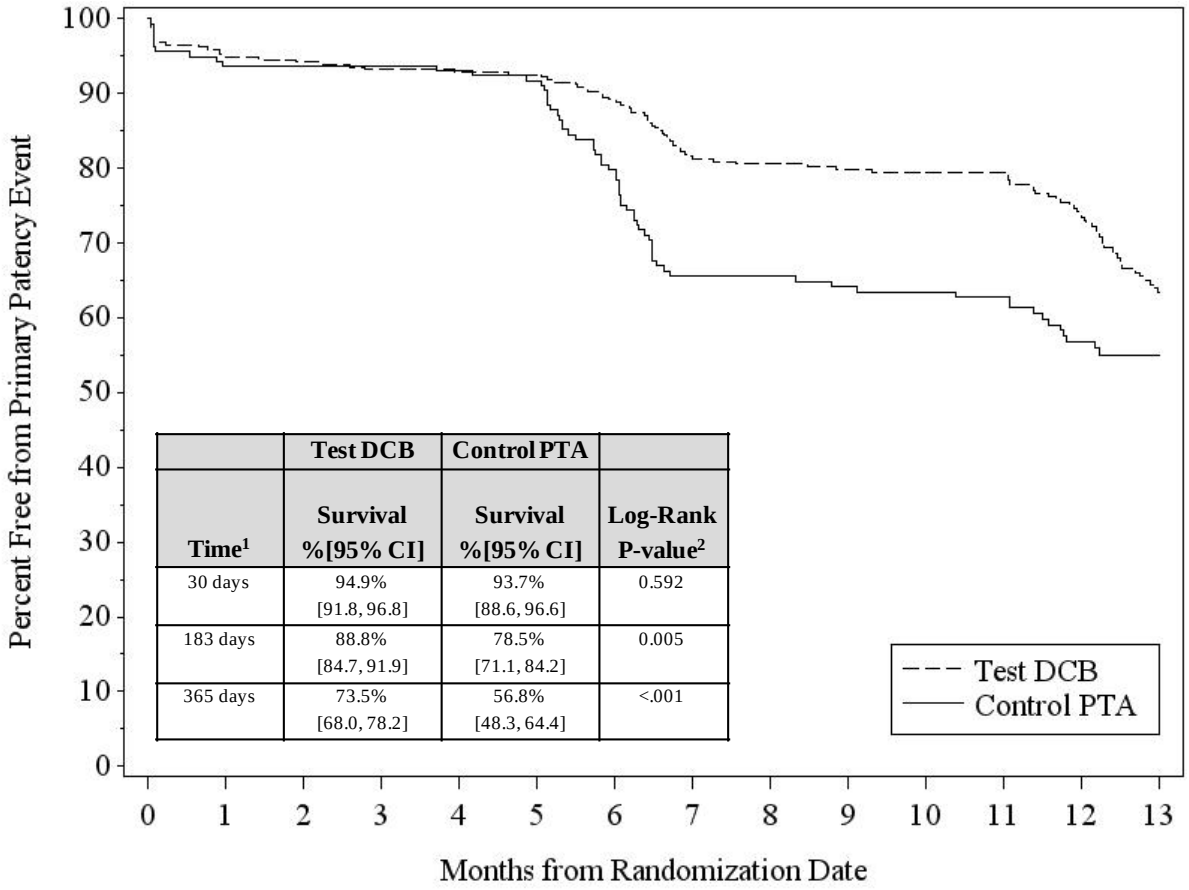
Table 15: Summary of Evaluation for Primary Patency at 12 Months in LEVANT 2

	Lutonix DCB	Control PTA
Analyzable for 12 month Primary Efficacy Endpoint (Primary Patency)	**83.5% (264/316)**	**84.4% (135/160)**
In-window Clinical Visit with analyzable DUS Completed, without TLR prior to end of 12m window	64.6% (204/316)	58.1% (93/160)
TLR prior to end of 12m window	11.1% (35/316)	15.0% (24/160)
Binary restenosis adjudicated on most recent prior DUS, without TLR or evaluable 12m DUS	3.5% (11/316)	6.3% (10/160)
Freedom from TLR and absence of binary restenosis determined by subsequent visit with analyzable DUS	4.4% (14/316)	5.0% (8/160)
Missing for 12 month Primary Efficacy Endpoint (Primary Patency)	**16.5% (52/316)**	**15.6% (25/160)**
Died without prior efficacy events	1.9% (6/316)	0.6% (1/160)
Withdrew without prior efficacy events	4.1% (13/316)	5.6% (9/160)
Lost-to-follow-up without prior efficacy events	1.9% (6/316)	0.6% (1/160)
Clinical info through 12m but DUS missing or non-evaluable (without prior efficacy events)	6.0% (19/316)	5.6% (9/160)

	Lutonix DCB	Control PTA
Missed visit at 12m without prior efficacy events (and no later demonstration of primary patency)	2.5% (8/316)	3.1% (5/160)

To address the impact of missing data on the findings for primary patency, additional analyses were conducted. Figure 5 presents a Kaplan-Meier survival curve for primary patency (freedom from binary restenosis and TLR). At 365 days, the primary patency rate was 73.5% for the Lutonix DCB group compared to 56.8% for the control PTA group ($p < 0.001$), consistent with the results of the primary proportion based analysis.

Figure 5: Kaplan-Meier Graph of Primary Patency (ITT Population)



	Test DCB	Control PTA	
Time[1]	Survival %[95% CI]	Survival %[95% CI]	Log-Rank P-value[2]
30 days	94.9% [91.8, 96.8]	93.7% [88.6, 96.6]	0.592
183 days	88.8% [84.7, 91.9]	78.5% [71.1, 84.2]	0.005
365 days	73.5% [68.0, 78.2]	56.8% [48.3, 64.4]	<.001

Primary patency was assessed using non-invasive Doppler imaging. Since the flow rate is conserved, the flow velocity must accelerate within a narrowed segment (compared to a non-diseased upstream vessel segment). The ratio of those peak systolic velocities (PSVR) has been reproducibly correlated to angiographic binary restenosis [9-11], with PSVR > 2.4 or ≥ 2.5 indicating angiographic 50%

restenosis (positive and negative predictive value 0.84 and 0.91). Therefore, as in several other prior femoropopliteal studies (e.g. [15]), PSVR ≥ 2.5 was prespecified as the threshold for restenosis.

The primary efficacy analysis included approximately 30 patients for whom the presence or absence of restenosis was adjudicated by the blinded core lab (based on absolute peak systolic velocity (PSV), waveforms, and distal turbulence) even though the absolute PSVR could not be determined (e.g., due to upstream stenosis). Three sensitivity analyses were therefore conducted based on application of strict PSVR thresholds (Table 16), including the original protocol definition of PSVR ≥ 2.5. Since PSVR 2.9-3.4 roughly correlates with 60-69% stenosis and PSVR 1.6-2.1 with 30-39% diameter stenosis [9, 10], results based on two additional thresholds for restenosis (PSVR ≥3.0 and ≥2.0) were also assessed. In all three analyses, primary patency rates favor the Lutonix DCB group over control PTA, with all but the lowest threshold for restenosis (~40% stenosis) reaching statistical significance. It is important to note that the conclusion of superior efficacy of Lutonix DCB over control PTA is preserved (64.0% vs. 51.2%, p = 0.017) when analyzed according to strict application of the protocol's PSVR ≥ 2.5 threshold for restenosis (i.e., censoring the 30 patients with indeterminate PSVR for whom presence or absence of restenosis was adjudicated by the core lab). Because PSVR has not been validated as a continuous variable, the analysis for different thresholds confirms the efficacy conclusions, since the results still discriminate the Lutonix DCB from control.

Table 16: Primary Patency Rate at 12 Months based on Alternative PSVR Thresholds (ITT Population)

Threshold for Binary Restenosis[1]	Lutonix DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
All Core Lab Adjudications (primary analysis)	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.015
DUS PSVR ≥ 3.0 (≥ ~60% stenosis)	68.3% (164/240) [62.4, 74.2]	56.1% (69/123) [47.3, 64.9]	12.2% [1.7, 22.8]	0.022
DUS PSVR ≥ 2.5 (per original protocol) (≥ 50% stenosis)	64.0% (155/242) [58.0, 70.1]	51.2% (65/127) [42.5, 59.9]	12.9% [2.3, 23.5]	0.017
DUS PSVR ≥ 2.0 (≥ ~40% stenosis)	53.2% (133/250) [47.0, 59.4]	45.0% (59/131) [36.5, 53.6]	8.2% [-2.4, 18.7]	0.130

[1] Primary Patency is defined as the absence of target lesion restenosis (totally occluded or application of the strict stated PSVR threshold) and target lesion revascularization (TLR).
[2] Nominal P-values based on asymptotic Likelihood Ratio test and CI for difference are provided without adjustment for multiplicity; hypothesis testing at alternative thresholds was not prespecified.

For patients without TLR and without evaluable DUS at 12 months, the primary analysis included prior DUS failures (since restenosis had already been documented) and late DUS successes (since the

treated segment was still patent afterwards). A sensitivity analysis based on application of different approaches to censoring is shown in Table 17. The difference in primary efficacy endpoint rates between groups is preserved independent of the method applied for inclusion of subjects as evaluable for primary patency, which suggests the findings favoring Lutonix DCB are not dependent on the method used to address patients missing diagnostic Doppler within the 12 month follow-up window.

Table 17: Sensitivity to Censoring Methods of Primary Patency Analyses at 12 Months

Method Applied for Inclusion of Patients as Evaluable for Primary Patency[1]	Lutonix DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value
Including late DUS success and early failures (primary analysis)	65.2% (172/264) [59.4, 70.9]	52.6% (71/135) [44.2, 61.0]	12.6% [2.4, 22.8]	0.015
Including ONLY in window DUS results	66.1% (158/239) [60.1, 72.1]	53.8% (63/117) [44.8, 62.9]	12.3% [1.4, 23.1]	0.026
Including late DUS successes (but not early failures)	68.0% (172/253) [62.2, 73.7]	56.8% (71/125) [48.1, 65.5]	11.2% [0.8, 21.6]	0.034
Including early DUS failure (but not late successes)	63.2% (158/250) [57.2, 69.2]	49.6% (63/127) [40.9, 58.3]	13.6% [3.0, 24.1]	0.012
Including late DUS success and early failures only if occurring after the post-procedural DUS in the 30-day follow-up window	65.6% (172/262) [59.9, 71.4]	53.4% (71/133) [44.9, 61.9]	12.3% [2.0, 22.5]	0.018

[1] Primary Patency is defined as freedom from target lesion restenosis (defined by core lab adjudication) and target lesion revascularization (TLR).

Worst case and tipping-point analyses were also conducted. Approximately 16% of subjects had missing data for Primary Efficacy Endpoint evaluation, 52 in the Lutonix DCB group and 25 in the control PTA group, consistent with the randomized allocation ratio. When all patients assigned Lutonix DCB who have missing data are presumed to have failed and all missing control patients are presumed to succeed, a worst case analysis fails to support Lutonix DCB efficacy.

However, the primary efficacy endpoint continues to be met if all missing subjects are presumed to be failures (difference between groups 10.1%, $p = 0.038$) and if all are presumed to be successes (difference between groups 10.9%, $p = 0.018$).

The tipping-point analysis is also supportive. If the control PTA rate in the evaluable cohort of 52.6% is assumed for the missing cohort, then the DCB rate for the missing cohort would have to be $\leq$ 44.2% (23/52) in order to fail the efficacy endpoint; this is 21% less than the 65.2% rate observed for the evaluable DCB cohort. Furthermore, if the Lutonix DCB rate of 65.2% is assumed for the missing cohort, then the PTA rate for the missing cohort would have to be $\geq$ 76.0% (19/25) in order to fail the efficacy endpoint; this is 23% higher than observed in the evaluable control PTA cohort. If

the primary efficacy success rate among missing subjects for DCB were assumed to be 30 of 52 (57.7%), which is below the lower limit (59.4%) of the 95% CI for the evaluable DCB cohort, then the superior primary patency is still demonstrated as long as 16 or less of the missing 25 PTA subjects (64.0%) are free from efficacy events, which is higher than the upper bound (61.0%) of the 95% CI for the evaluable control PTA cohort. In general, a difference in success rates significantly favoring PTA over DCB would have to be observed for missing subjects in order to fail to meet the efficacy endpoint. Taken together with the analyses suggesting results are independent of methods for handling data that is missing because of the timing of evaluations (including Figure 5 and Table 17), the tipping-point analysis demonstrates a robust observed treatment effect.

5.9.2 Composite Safety Endpoint

The primary safety endpoint was a composite of freedom from all-cause perioperative (≤30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb re-intervention, and index-limb-related death. Overall, 90.5% (286/316) test DCB subjects and 89.4% (143/160) control PTA subjects were evaluable for primary safety endpoint testing.

The proportion of subjects free from any safety event in the test group was 83.9% compared to 79.0% in the control group at 12 months, and noninferior safety was demonstrated (p = 0.005) with a noninferiority margin of 5% (Table 18).

Table 18: Primary Safety Endpoint Success Rate at 1 year (ITT Population)

Measure	Lutonix DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
Freedom from Primary Safety Event[1]	83.9% (240/286) [79.7, 88.2]	79.0% (113/143) [72.3, 85.7]	4.9% [-2.6, 12.3]	0.005

[1] Composite freedom from safety events, including all-cause perioperative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death.
[2] P-value and CI for difference based on a Farrington-Manning method. Confidence intervals for groups are asymptotic. Margin of non-inferiority 5%.

Safety events are shown by treatment group in Table 19. There were no perioperative or index limb related deaths. There was a single amputation and a single AV fistula surgery (in the DCB group). Target limb interventions included TLR (12.3% vs. 16.8%), surgical bypass (0.7% vs. 0.7%, also counted as a TLR), non-TLR TVR (1.1% vs. 1.4%) and interventions in other vessels of the index limb (2.1% vs. 2.9%).

Table 19: Safety Events through 1 Year (ITT Population)

Safety Event *(subject may have more than one event)*	**Test DCB %(n/N) [95% CI]**	**Control PTA %(n/N) [95% CI]**
Perioperative (<=30) Death	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]
Index Limb Related Death at 12 Months	0.0% (0/285) [0.0, 0.0]	0.0% (0/140) [0.0, 0.0]
Amputation at 12 Months	0.3% (1/286) [0.0, 1.0]	0.0% (0/140) [0.0, 0.0]
AV Fistula Surgery at 12 months	0.4% (1/285) [0.0, 1.0]	0.0% (0/140) [0.0, 0.0]
Surgical Bypass at 12 months	0.7% (2/285) [0.0, 1.7]	0.7% (1/140) [0.0, 2.1]
Total TLR at 12 Months	12.3% (35/285) [8.5, 16.1]	16.8% (24/143) [10.7, 22.9]
Non-TLR TVR at 12 months	1.1% (3/285) [0.0, 2.2]	1.4% (2/143) [0.0, 3.3]
Index limb interventions in non-target vessels at 12 months	2.1% (6/285) [0.4, 3.8]	2.9% (4/140) [0.1, 5.6]

The primary safety endpoint findings are preserved after adjusting for covariates (unadjusted Odds Ratio (OR) = 0.72, p=0.212 vs. adjusted OR = 0.70, p=0.219).

5.9.2.1 Sensitivity Analyses of Composite Safety Endpoint

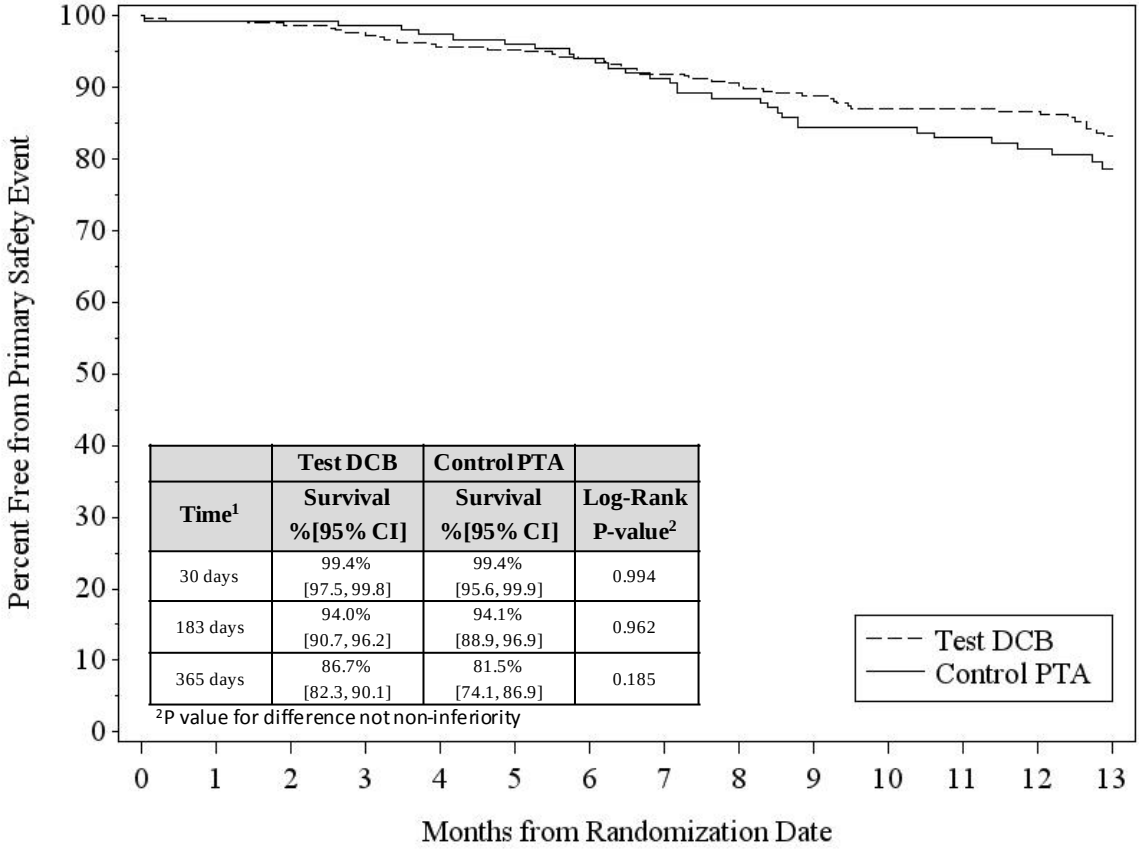
Overall, 47 patients (9.9%) were excluded from analysis of the composite safety endpoint (Table 20). In the Lutonix DCB group and control PTA group, respectively, 7.3% (n=23) and 8.1% (n=13) died, withdrew, or were lost-to-follow-up without prior safety events. An additional 2.2% (n=7) and 2.5% (n=4) had missed visits at 12 months without prior safety events or later evidence of success.

Table 20: Summary of Evaluation for Primary Safety at 12 Months in LEVANT 2

	Lutonix DCB	Control PTA
Analyzable for 12 month Primary Safety Endpoint	**90.5% (286/316)**	**89.4% (143/160)**
In-window Clinical Visit and/or failed prior to 395 days	81.0% (256/316)	78.8% (126/16)
Freedom from safety events through 395 days demonstrated by subsequent contact	9.5% (30/316)	10.6% (17/160)
Missing for 12 month Primary Safety Endpoint	**9.5% (30/316)**	**10.6% (17/160)**
Died without prior safety events	1.3% (4/316)	1.3% (2/160)
Withdrew without prior safety events	4.1% (13/316)	6.3% (10/160)
Lost-to-follow-up without prior safety events	1.9% (6/316)	0.6% (1/160)
Missed visit at 12m without prior safety events (and no later evidence of success through 12m)	2.2% (7/316)	2.5% (4/160)

To address the impact of missing data on the primary findings for composite safety, additional analyses were conducted. Figure 6 presents a Kaplan-Meier survival curve for the composite safety endpoint. At 365 days, 86.7% of Lutonix DCB patients and 81.5% of control PTA patients were free from safety events, supporting the findings of the primary analysis.

Figure 6: Kaplan-Meier Graph of Primary Safety Endpoint Success Rate (ITT Population)



	Test DCB	Control PTA	
Time[1]	Survival %[95% CI]	Survival %[95% CI]	Log-Rank P-value[2]
30 days	99.4% [97.5, 99.8]	99.4% [95.6, 99.9]	0.994
183 days	94.0% [90.7, 96.2]	94.1% [88.9, 96.9]	0.962
365 days	86.7% [82.3, 90.1]	81.5% [74.1, 86.9]	0.185

[2]P value for difference not non-inferiority

Worst case and tipping-point analyses have also been conducted. For primary safety evaluation, approximately 10% of the subjects were missing data, including 30 in the Lutonix DCB group and 17 in the control PTA group. Non-inferiority is not demonstrated under worst case assumptions (wherein all missing test subjects are presumed to have failed and all missing control subjects are presumed to succeed) due to the large number of imputed worst cases.

The safety endpoint continues to be met if all missing subjects are presumed to be failures ($p = 0.007$) and if all are presumed to be successes ($p = 0.004$).

In order for the primary safety analysis to fail there would need to be more than 15% more successes among the 17 missing PTA subjects than the 30 missing DCB subjects. For example, if 15 of 17 (88%) missing control PTA subjects were free from primary safety events (a success rate among missing controls that is higher than the upper limit of the 95% CI for the evaluable cohort of 85.7%), DCB would continue to demonstrate non-inferior safety as long as at least 20 of 30 (66.7%) were free from safety events (a success rate among missing test subjects much lower than the lower limit of the 95% CI for the evaluable DCB cohort of 79.7%). Therefore, the conclusion of non-inferior safety is robust.

5.9.3 Per Protocol Analysis: Primary Efficacy and Safety Endpoints

The prespecified PP dataset excluded subjects for whom treatment did not follow the protocol defined procedures or inclusion criteria were violated that would be expected to affect primary outcomes. As prespecified in the SAP, the former group included core-lab adjudicated geographic miss (not treating the entire predilated injury segment with the as-randomized study device), which was intended to ensure drug delivery to the entirety of the pre-dilated injury segment. Geographic miss relates to incomplete coverage of the lesion. Geographic miss was reported by the angiographic core lab and not the investigation site. Since the core lab was blinded to the treatment arm, it inadvertently reported geographic miss for PTA. The purpose of PTA was standard practice. There was an imbalance in the rate of geographic miss between treatment groups, with 7.6% (24/316) test DCB and 21.9% (35/160) control PTA subjects excluded for this reason. These were identified by the blinded angiographic core lab and not reported by the site. Subjects were also excluded (for test vs. control groups respectively) for assigned treatment not given (0% vs. 0%), treatment without predilatation (0% vs. 0%), outflow treatment (0.6% (2/316) vs. 1.3% (2/160)), thrombectomy prior to randomization (0% vs. 0.6% (1/160)), and site-reported lesion length > 15cm (0% vs. 0%). Of ITT subjects, 92.1% (291/316) test DCB and 76.3% (122/160) control PTA subjects are included in the prespecified PP population. The largest reason for exclusion was geographic miss, as adjudicated by the blinded core-lab, and interpretation of outcomes for this PP subset is confounded by the observation that it occurred much more commonly in the control than the test group.

It was observed that patients included and excluded from the prespecified PP dataset had different lesion characteristics at baseline. Baseline (pre-randomization) percent diameter stenosis (%DS) was 79.6 ± 14.9% (median 80.0%) for patients included in the PP population compared to 87.6 ± 12.2% (median 89.0%) for patients excluded from PP (difference 8.0%, $p < 0.001$). Since baseline %DS is a covariate that correlates with primary efficacy endpoint failure ($p < 0.001$), the observation that more of these patients were excluded from the control group than from the test group complicates interpretation of the prespecified PP analysis. Although baseline lesion characteristics differed, procedural results were similar for both PP and not-PP cohorts. Post-procedural %DS was 20.9 ± 9.7% (median 22.0%) for patients included in PP dataset compared to 21.2 ± 11.0% (median 22.0%) for patients excluded from the PP dataset (difference 0.3%, $p = 0.804$). Therefore, patients included and excluded from the PP dataset were treated similarly during the index procedure, and results over time may reflect baseline lesion characteristics rather than treatment. The prespecified PP analysis is not robust given the imbalance in exclusion and the observed difference (pre-randomization) in treated lesions for excluded and included subjects.

Therefore, a second Per Protocol (PP2) Population was defined post-hoc that included subjects with geographic miss and instead excluded subjects not meeting protocol-defined lesion entry criteria by core-lab analysis. ITT subjects excluded from PP2 for this reason include lesion length > 150 mm (2.5% (8/316) vs. 3.1% (5/160)) and RVD < 4 mm (13.0% (41/316) vs. 10.0% (16/160)) for test and control groups respectively. Also excluded are the same subjects excluded from PP for assigned

treatment not given (0%), treatment without predilatation (0%), outflow treatment (0.6% vs.1.3%), and thrombectomy prior to randomization (0% vs. 0.6%). Of ITT subjects, 83.9% (265/316) test DCB and 85.0% (136/160) control PTA are included in this more balanced PP2 population.

In the post-hoc PP2 Population (excluding core lab lesion length > 150mm and diameter < 4mm instead of geographic miss), superiority of the efficacy endpoint (Table 21) non-inferiority of the safety endpoint (Table 22) was demonstrated.

Table 21: Primary Patency[1] at 1 Year (Per Protocol Populations PP & PP2)

Population	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
PP[3]	65.3% (160/245) [59.3, 71.3]	56.0% (56/100) [46.3, 65.7]	9.3% [-2.1, 20.7]	0.107
PP2[4]	67.6% (152/225) [61.4, 73.7]	52.2% (60/115) [43.0, 61.3]	15.4% [4.4, 26.4]	0.006

[1] Primary Patency is defined as freedom from target lesion restenosis (defined by core lab adjudication) and target lesion revascularization (TLR).
[2] Based on asymptotic Likelihood Ratio test. CIs for groups and difference are asymptotic.
[3] PP Population prespecified to exclude core lab geographic miss, assigned treatment not given, no predilatation, outflow artery treatment, thrombectomy prior to randomization, site reported length > 150mm.
[4] PP2 Population defined post-hoc to exclude core lab lesions length >150mm and diameter < 4mm, assigned treatment not given, no predilatation, outflow artery treatment, thrombectomy prior to randomization.

Table 22: Primary Safety Endpoint Success Rate[1] at 1 year (Per Protocol Populations PP and PP2)

Population	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
PP[3]	83.7% (221/264) [79.3, 88.2]	83.0% (88/106) [75.9, 90.2]	0.7% [-7.3, 8.7]	0.080
PP2[4]	84.2% (202/240) [79.5, 88.8]	79.3% (96/121) [72.1, 86.6]	4.8% [-3.2, 12.9]	0.008

[1] Composite freedom from safety events, including all-cause perioperative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death.
[2] P-value and CI for difference based on a Farrington-Manning method. Confidence intervals for groups are asymptotic. Margin of non-inferiority 5%.
[3] PP Population prespecified to exclude core lab geographic miss, assigned treatment not given, no predilatation, outflow artery treatment, thrombectomy prior to randomization, site reported length > 150mm.
[4] PP2 Population specified post-hoc to exclude core lab lesions length >150mm and diameter < 4mm, assigned treatment not given, no predilatation, outflow artery treatment, thrombectomy prior to randomization.

5.9.4 Subgroup Analysis of the Primary Efficacy and Safety Endpoints

Figure 7 and Figure 8 provide forest plots of primary patency and composite safety by patient subgroup, respectively. Overall, the treatment effect for primary patency and composite safety was generally consistent across most subgroups as reflected by the overlap in CIs.

As in most clinical trials, LEVANT 2 was not powered to statistically examine differences in results between subgroups. Unexpected results were observed within certain subsets. For example, among subjects with total occlusions, the treatment effect as assessed by primary efficacy was greater but as assessed by primary safety was less than that observed for the ITT population. An unexpected inverse endpoint correlation was also observed for gender subsets; the treatment effect as assessed by primary safety was greater but as assessed by efficacy was less for females compared to males. The observed treatment effect also appeared larger in EU than in the US.

The protocol prespecified statistical testing of the primary endpoints for interaction with geography (p value for interaction = 0.1219 for efficacy and 0.0205 for safety). Geography and gender interactions are explored in detail below in Section 5.17.1. The differences are largely explained by differences in the observed treatment effects for US females compared to EU females. For primary patency, smoking status, rather than gender or geography, appears to be responsible for the interaction. For composite safety, very poor results were observed for EU women assigned to the control PTA group. The study was not powered to test interactions or differences between the test and control arms within regional, gender, and smoking subgroups. Therefore it is not unlikely that, by chance, different treatment effects are observed in subsets[33].

Figure 7: Primary Patency by Patient Subgroup

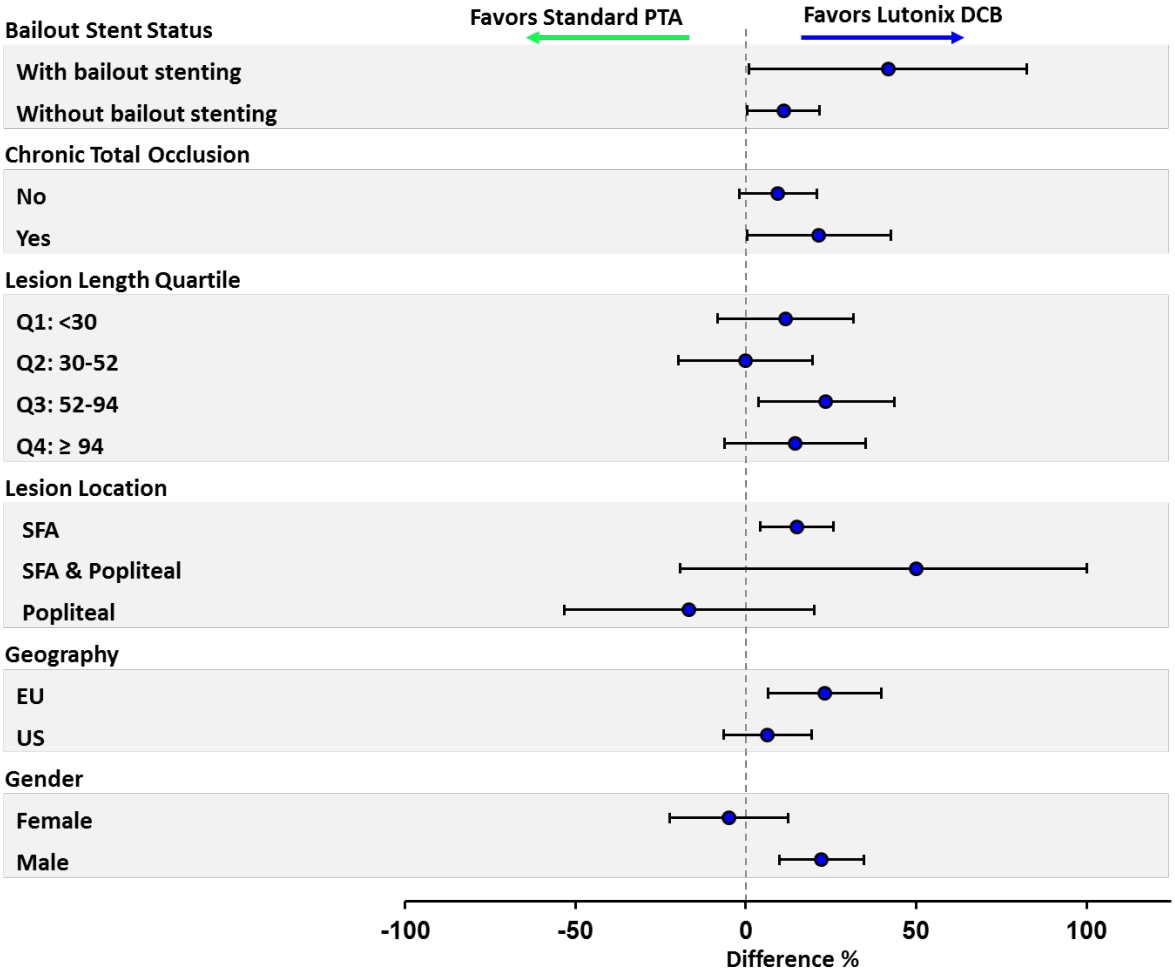
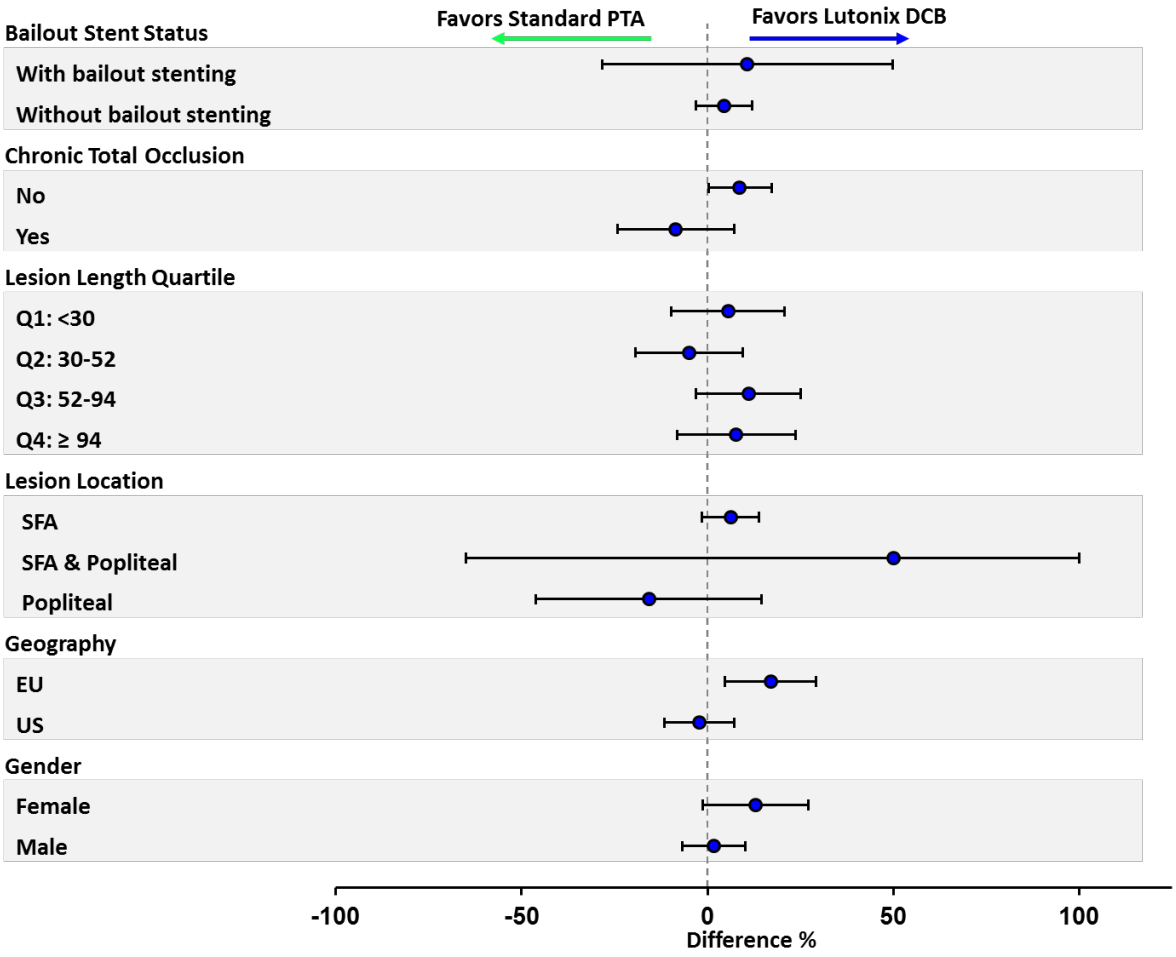


Figure 8: Composite Safety by Patient Subgroup



5.10 Secondary Endpoints

Since both primary endpoints met prespecified criteria for success, the protocol specified hierarchical testing of total 12 month TLR, 12 month TVR and 12 month composite safety for Lutonix DCB superiority. All three endpoints trended in favor of Lutonix DCB but did not reach statistical significance (Table 23).

Table 23: Results of Hypothesis Testing for Secondary Endpoints (ITT Population)

Measure	Lutonix DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[1]
Total TLR at 12 Months[3]	12.3% (35/285) [8.5, 16.1]	16.8% (24/143) [10.7, 22.9]	-4.5% [-11.7, 2.7]	0.208
Total TVR at 12 Months[3]	13.3% (38/285) [9.4, 17.3]	18.2% (26/143) [11.9, 24.5]	-4.8% [-12.3, 2.6]	0.190
Composite Safety Events[2] at 12 Months	16.1% (46/286) [11.8, 20.3]	21.0% (30/143) [14.3, 27.7]	-4.9% [-12.8, 3.0]	0.215

[1] Based on asymptotic Likelihood Ratio test. CIs for groups and difference are asymptotic.
[2] The composite event is all-cause death at 30 days, and amputation, index-limb re-intervention, or index-limb-related death at 12 months. Test is for difference not non-inferiority.
[3] Includes 2 Lutonix DCB and 1 control PTA with surgical bypass of the target vessel.

5.11 Other Secondary Endpoints

Additional secondary endpoints were analyzed to explore trends over time and the clinical meaningfulness of the findings with the primary endpoints. Adjustments for multiplicity were not performed given the descriptive purpose of the analyses.

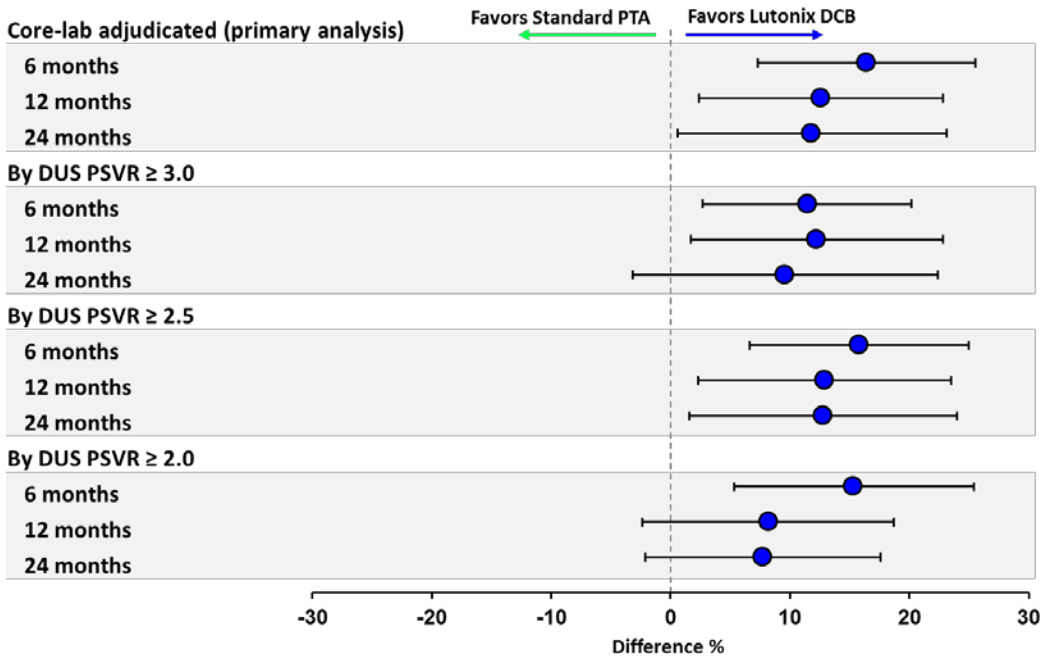
Interim data through 24 months is included but should be interpreted with caution. Success, but not failure, requires freedom-from-events to be demonstrated by contact after the 24 month follow-up window opens. Although only 40.8% of randomized patients have 24 month follow-up, 50.0% are evaluable for safety including all prior failures. Patency success also requires diagnostic DUS in the 24 month window. Currently, only 24.6% of subjects have adjudicated DUS results at 24 months. Including all prior failures, 50.2% of subjects are evaluable for primary patency endpoint at 24 months. Therefore, failures are more prevalent in the evaluable cohort (since all prior and interim failures are evaluable), while successes are more prevalent in the censored cohort (since they remain missing until after DUS at 24 months).

5.11.1 Primary and Alternative Patency

The difference between groups in the rate of primary patency (based on all core lab adjudications) and the rate based on strict application of alternative PSVR thresholds for restenosis are presented for

each follow-up time window in (Figure 9) below. The Lutonix DCB group had a consistently higher rate of primary patency compared to the control PTA at 6 months, regardless of the threshold for DUS restenosis applied. At 12 months, the test DCB group maintained higher patency results based on all core-lab adjudications and alternative thresholds for binary restenosis DUS PSVR ≥ 2.5 (correlated with ≥ 50% angiographic diameter stenosis) or 3.0 (correlated with approximately ≥ 60% diameter stenosis). Based on preliminary 24 month data, the difference between treatment groups in primary patency is preserved for both the primary analysis including all adjudications (difference of 11.8%, p = 0.047) and the original protocol's strict application of PSVR 2.5 (difference of 12.8%, p = 0.032).

Figure 9: Difference between Groups in Primary and Alternative Patency at 6, 12, and interim 24 Months

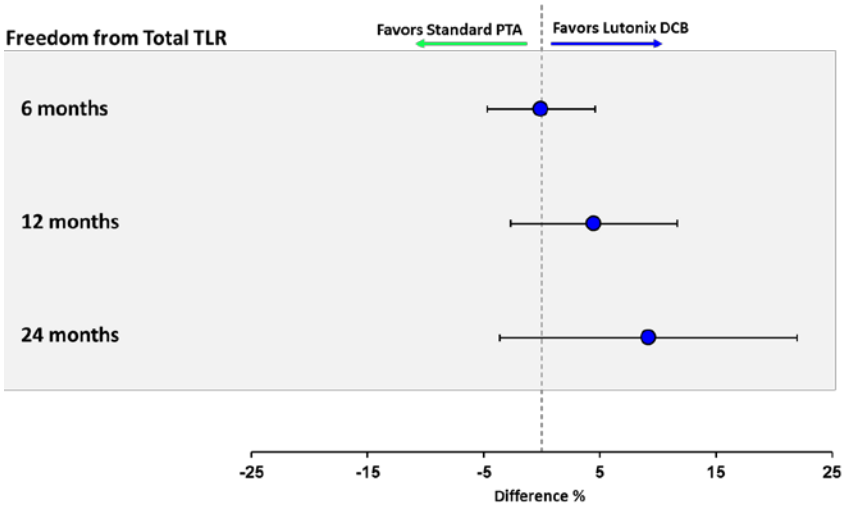


Based on asymptotic Likelihood Ratio test. CIs for groups and difference are asymptotic.

5.11.2 Freedom from TLR

Although the absolute differences do not reach significance, the point estimates favoring Lutonix DCB over control PTA in freedom from TLR increase over time (Figure 10).

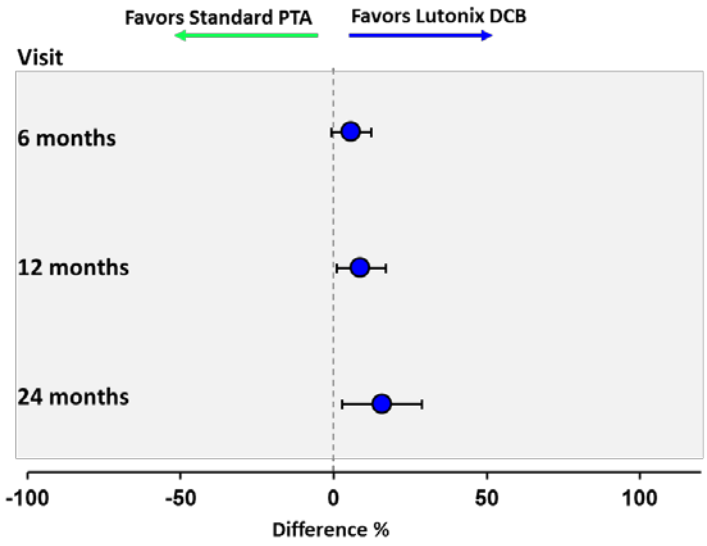
Figure 10: Difference between Groups in Freedom from TLR at 6, 12, and interim 24 months



In recent PMA studies of new devices for treatment of femoropopliteal artery disease by percutaneous intervention [15, 16], bailout stenting in the control arm was counted as an immediate endpoint failure. The potential for bias by unblinded treating physicians was minimized in the present study by (1) minimizing stenting by predilation and assessment prior to randomization, (2) incorporating stricter criteria for bailout stenting, and (3) not considering stenting to be a failure of any endpoint, i.e., bailout stenting is not considered a TLR or a primary efficacy failure in the primary analysis. This difference complicates comparability of the present study to historic results.

Even with the low stent rate (4.0%) that was observed in LEVANT 2, if bail-out stenting were to have been counted as a TLR (since the intended treatment was balloon only as in prior stent PMA studies), then a post hoc significant difference in freedom-from TLR rates would have been observed at 12 months (85.3% for test DCB vs. 76.4% for control, p = 0.024); rate differences are shown in Figure 11.

Figure 11: Difference in Freedom from TLR at 6, 12, and 24 months, Counting Bailout Stent as a TLR



5.11.3 Functional Endpoints

The ABI values, Rutherford scores, and walking impairment (WIQ) scores each significantly improved ($p < 0.001$) from before treatment to 12 months in both the DCB and PTA groups, with most numerically favoring the DCB group (Figure 12). Only the improvement in the walking distance component of WIQ demonstrated a significant difference between groups at 12 months (DCB-PTA = 9.3; 95% CI [1.6, 17.0]). At 12 months, 88.2% of Lutonix DCB patients and 82.4% of control PTA patients had improved Rutherford Class compared to baseline.

Although changes in QOL and functional parameters were similar for both groups, interpretation of these measures is complicated by interim reinterventions, comorbidities, and progressive disease in non-treated vessels. A post-hoc analysis of sustained improvement in Rutherford class without target vessel reintervention demonstrated a significant benefit in favor of the DCB group compared to the PTA group at 12 months (76.2% vs. 66.6%; p=0.041; Figure 13).

Figure 12: Difference in Functional Endpoints at 12 Months

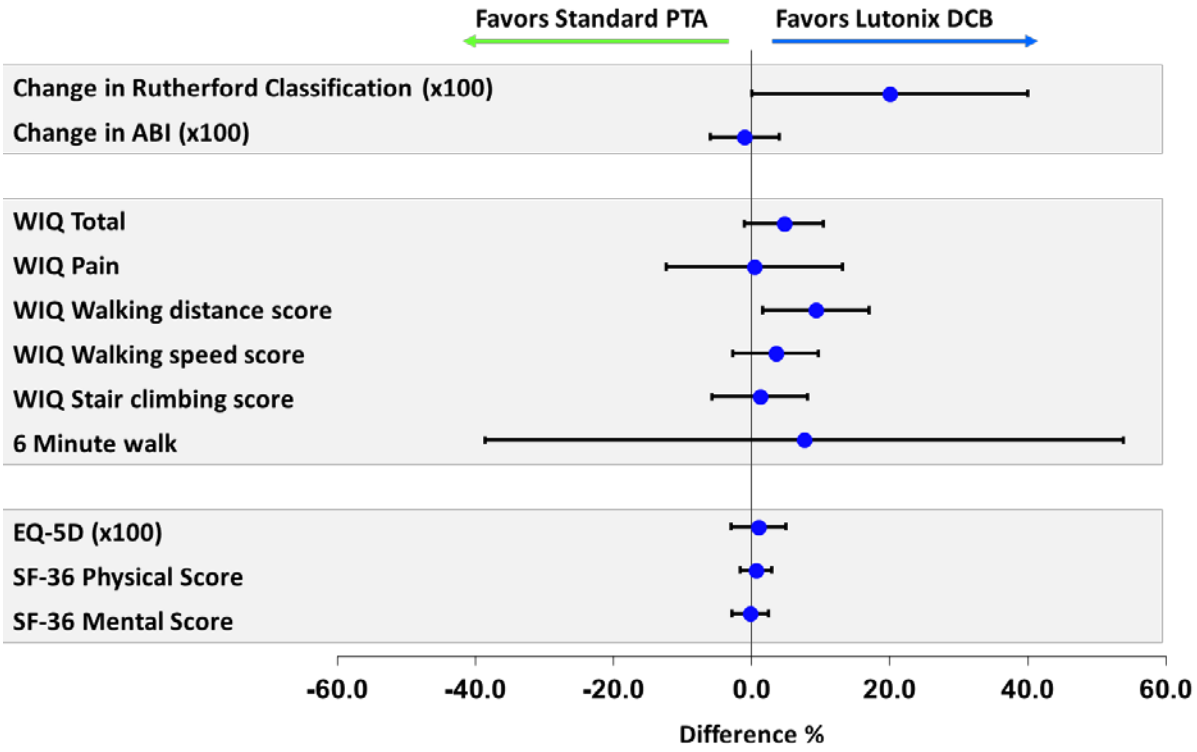
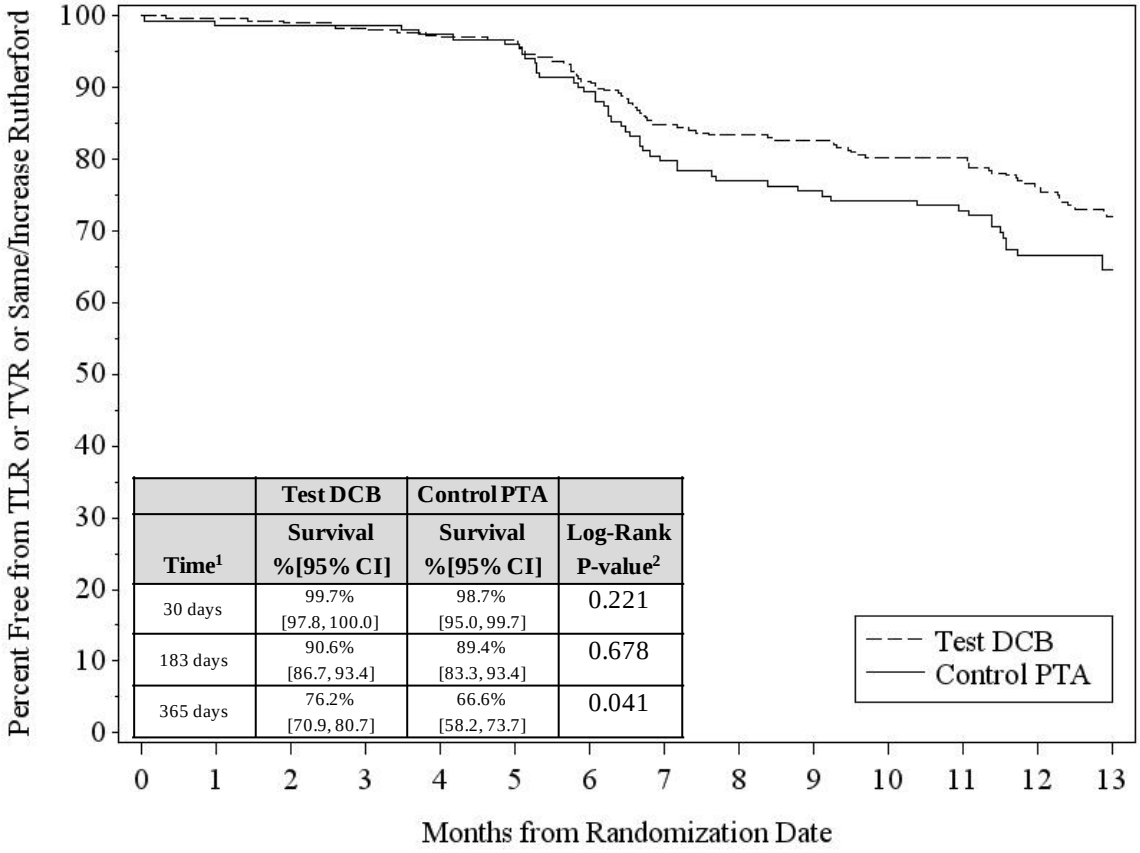


Figure 13: Sustained Improvement in Rutherford Class Without Reintervention



	Test DCB	Control PTA	
Time[1]	Survival %[95% CI]	Survival %[95% CI]	Log-Rank P-value[2]
30 days	99.7% [97.8, 100.0]	98.7% [95.0, 99.7]	0.221
183 days	90.6% [86.7, 93.4]	89.4% [83.3, 93.4]	0.678
365 days	76.2% [70.9, 80.7]	66.6% [58.2, 73.7]	0.041

5.11.4 Device, Technical, and Procedural Success

Procedural success (≤30% residual stenosis by independent core lab analysis without serious adverse events during the index procedure), technical success (device success and visual estimate ≤30% residual stenosis without deploying a stent), and device success (ability to deploy, inflate, and retrieve the device without abnormalities) were all similar between treatment groups (Table 24). The procedural success rates were comparable for Lutonix DCB and Control PTA, 88.9% vs. 86.8%, p = 0.5.

Table 24: Device, Technical, and Procedural Success (ITT Population)

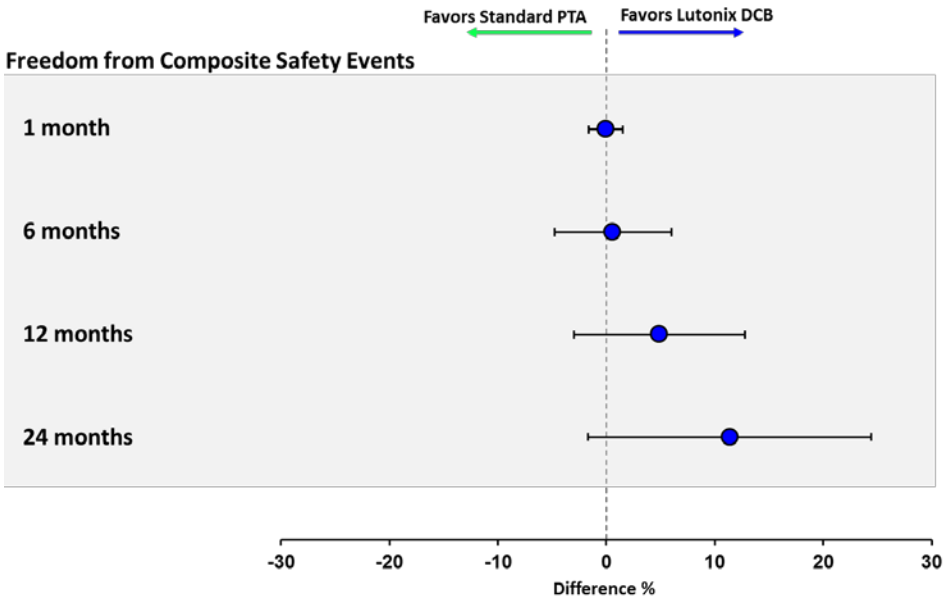
Variable	Lutonix DCB	Control PTA	P-value[1]
Device Success, % (n/N)	99.5% (430/432)	100% (180/180)	0.361
Technical Success (Core Lab, All Lesions), % (n/N)	89.2% (282/316)	86.8% (138/159)	0.431
Procedural Success (Core Lab, All Lesions), % (n/N)	88.9% (281/316)	86.8% (138/159)	0.497

[1] X^2-tests for proportions

5.11.5 Composite Safety Endpoint

The composite safety endpoint is defined as freedom from all-cause 30-day death and at 12 months from index-limb related death, amputation, and reintervention. This endpoint was powered for non-inferiority at 12 months; although the absolute difference does not reach significance, the point estimates favoring Lutonix DCB over control PTA increase over time (Figure 14).

Figure 14: Difference between Groups in Freedom from Safety Events at 1, 6, 12, and interim 24 months



5.11.6 Secondary Safety Endpoints

Table 25 summarizes key safety endpoints prespecified for analysis in LEVANT 2. No significant differences were observed between test and control groups in any of the secondary safety endpoints at 1, 6, and 12 months. Major vascular complications and cardiovascular hospitalizations are further in Section 6 in the context of additional Lutonix DCB data from the LEVANT 2 continued access/safety registry and historic rates for the enrolled population with symptomatic PAD. Interim rates at 24 months are also provided but should be interpreted with caution, since all prior failures are included and only 41% of patients have had 24 month follow-up and not all events have been adjudicated. No differences were observed between the Lutonix DCB group and control PTA that suggest worse safety outcomes for DCB.

Table 25: Secondary Safety Endpoints by Timepoint in LEVANT 2

Outcome	Visit	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
Freedom from Composite Safety Events[1]	1 Month	99.4% (306/308) [98.5, 100.0]	99.4% (154/155) [98.1, 100.0]	-0.0% [-1.6, 1.5]	0.996
	6 Months	92.0% (275/299) [88.9, 95.1]	91.4% (138/151) [86.9, 95.9]	0.6% [-4.8, 6.0]	0.832
	12 Months	83.9% (240/286) [79.7, 88.2]	79.0% (113/143) [72.3, 85.7]	4.9% [-3.0, 12.8]	0.215
	24 Months	68.2% (107/157) [60.9, 75.4]	56.8% (46/81) [46.0, 67.6]	11.4% [-1.7, 24.4]	0.085
Death	1 Month	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]	0.0%	N/A
	6 Months	0.7% (2/301) [0.0, 1.6]	1.3% (2/152) [0.0, 3.1]	-0.7% [-2.7, 1.4]	0.497
	12 Months	2.4% (7/290) [0.6, 4.2]	2.8% (4/144) [0.1, 5.5]	-0.4% [-3.6, 2.8]	0.822
	24 Months[3]	6.9% (10/144) [2.8, 11.1]	6.6% (5/76) [1.0, 12.2]	0.4% [-6.6, 7.3]	0.918
Major Amputation	1 Month	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]	0.0%	N/A
	6 Months	0.3% (1/299) [0.0, 1.0]	0.0% (0/151) [0.0, 0.0]	0.3% [-0.3, 1.0]	0.366
	12 Months	0.3% (1/286) [0.0, 1.0]	0.0% (0/140) [0.0, 0.0]	0.3% [-0.3, 1.0]	0.372
	24 Months	0.7% (1/135) [0.0, 2.2]	0.0% (0/71) [0.0, 0.0]	0.7% [-0.7, 2.2]	0.357
Amputation Free Survival	1 Month	100.0% (308/308) [100.0, 100.0]	100.0% (155/155) [100.0, 100.0]	0.0%	N/A
	6 Months	99.3% (298/300) [98.4, 100.0]	98.7% (150/152) [96.9, 100.0]	0.6% [-1.4, 2.7]	0.499
	12 Months	97.6% (283/290) [95.8, 99.4]	97.2% (140/144) [94.5, 99.9]	0.4% [-2.8, 3.6]	0.822
	24 Months	93.1% (134/144) [88.9, 97.2]	93.4% (71/76) [87.8, 99.0]	-0.4% [-7.3, 6.6]	0.918

Outcome	Visit	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]	P-value[2]
Total TVR	1 Month	0.3% (1/308) [0.0, 1.0]	0.6% (1/155) [0.0, 1.9]	-0.3% [-1.7, 1.1]	0.630
	6 Months	6.7% (20/298) [3.9, 9.6]	7.9% (12/151) [3.6, 12.3]	-1.2% [-6.4, 3.9]	0.633
	12 Months	13.3% (38/285) [9.4, 17.3]	18.2% (26/143) [11.9, 24.5]	-4.8% [-12.3, 2.6]	0.190
	24 Months	28.3% (43/152) [21.1, 35.4]	39.2% (31/79) [28.5, 50.0]	-11.0% [-23.9, 2.0]	0.093
Reintervention for Thrombosis	1 Month	0.3% (1/308) [0.0, 1.0]	0.0% (0/155) [0.0, 0.0]	0.3% [-0.3, 1.0]	0.366
	6 Months	0.3% (1/298) [0.0, 1.0]	0.7% (1/151) [0.0, 2.0]	-0.3% [-1.8, 1.1]	0.633
	12 Months	0.4% (1/285) [0.0, 1.0]	0.7% (1/140) [0.0, 2.1]	-0.4% [-1.9, 1.2]	0.618
	24 Months	0.7% (1/135) [0.0, 2.2]	1.4% (1/71) [0.0, 4.1]	-0.7% [-3.8, 2.4]	0.651
Cardiovascular Hospitalization	1 Month	0.0% (0/308) [0.0, 0.0]	0.0% (0/155) [0.0, 0.0]	0.0%	N/A
	6 Months	5.7% (17/298) [3.1, 8.3]	2.0% (3/151) [0.0, 4.2]	3.7% [0.3, 7.2]	0.054
	12 Months	9.1% (26/285) [5.8, 12.5]	7.1% (10/140) [2.9, 11.4]	2.0% [-3.4, 7.4]	0.485
	24 Months	25.5% (38/149) [18.5, 32.5]	25.3% (20/79) [15.7, 34.9]	0.2% [-11.7, 12.1]	0.975
Major Vascular Complications[4]	1 Month	4.2% (13/308) [2.0, 6.5]	1.3% (2/156) [0.0, 3.0]	2.9% [0.1, 5.8]	0.068
	6 Months	5.4% (16/298) [2.8, 7.9]	2.6% (4/152) [0.1, 5.2]	2.7% [-0.9, 6.3]	0.164
	12 Months	6.3% (18/285) [3.5, 9.1]	4.9% (7/142) [1.4, 8.5]	1.4% [-3.2, 5.9]	0.560
	24 Months	13.6% (20/147) [8.1, 19.1]	10.7% (8/75) [3.7, 17.7]	2.9% [-6.0, 11.9]	0.528

[1] The composite event is all-cause death at 30 days, and amputation, index-limb re-intervention, or index-limb-related death.
[2] Based on asymptotic Likelihood Ratio test. CIs for groups and difference are asymptotic.
[3] Deaths adjudicated by the CEC. An additional 6 test DCB and 2 control PTA deaths have been reported between 12 and 24 months that are still pending CEC adjudication, for a cumulative total of 16 test and 7 control through 24 months.
[4] Major Vascular Complication is defined as serious Hematoma at access site >5 cm, False aneurysm, AV fistula, Retroperitoneal bleed, Peripheral ischemia/nerve injury, Any transfusion required will be reported as a vascular complication unless clinical indication clearly other than catheterization complication, Vascular surgical repair.

5.12 CEC Adjudicated Adverse EVents

An overview of the number of adverse events and summaries of patients with adverse events occurring in LEVANT 2 through the 24 month follow-up window is provided in Table 26. All adverse events through 12 months have been adjudicated by the CEC, but adjudication of later events is ongoing. During CEC adjudication, multiple site-reported events could have been combined into a single event and some events were adjudicated as non-events. Overall, there was little difference between groups in incidence for any AE category.

Table 26: Overview of CEC-Adjudicated Adverse Events through the 24-Month Follow-up Window in LEVANT 2 (AT Population)

Adverse Event Type	Lutonix DCB		PTA	
	n events	N=316 %(n patients)	n events	N=160 %(n patients)
CEC-adjudicated Adverse Events	726	75.9% (240)	338	68.8% (110)
Site-Reported Adverse Events	1007	84.5% (267)	466	74.4% (119)
CEC-adjudicated Probably or Highly Probably Device-Related Adverse Events	59	15.5% (49)	37	20.0% (32)
Site-Reported Probably or Highly Probably Device-Related Adverse Events	33	9.8% (31)	11	6.9% (11)
CEC-adjudicated Probably or Highly Probably Procedure-Related Adverse Events	113	25.9% (82)	55	26.9% (43)
Site-Reported Probably or Highly Probably Procedure-Related Adverse Events	84	20.3% (64)	34	18.8% (30)
CEC-adjudicated Serious Adverse Events	338	53.5% (169)	169	50.0% (80)
Site-Reported Serious Adverse Events	420	60.4% (191)	235	55.6% (89)
CEC-adjudicated Probably or Highly Probably Device-Related Serious Adverse Events	43	11.1% (35)	33	18.1% (29)
Site-Reported Probably or Highly Probably Device-Related Serious Adverse Events	12	3.5% (11)	6	3.8% (6)
CEC-adjudicated Probably or Highly Probably Procedure-Related Serious Adverse Events	62	15.2% (48)	41	21.3% (34)
Site-Reported Probably or Highly Probably Procedure-Related Serious Adverse Events	25	6.3% (20)	14	8.8% (14)
CEC-Adjudicated Deaths*	10	3.2% (10)	5	3.1% (5)
Site-Reported Deaths*	16	5.1% (16)	7	4.4% (7)

Adverse Event Type	Lutonix DCB		PTA	
	n events	N=316 %(n patients)	n events	N=160 %(n patients)

* Includes events reported through end of 24 month window. CEC adjudication of 24-month events is ongoing; 6 test DCB and 2 control PTA site-reported deaths have not yet been CEC adjudicated.

The most frequently reported (≥5% in either treatment group) adverse events through 24 months are summarized in Table 27. The overall frequency of individual adverse events was similar for test and control groups and not unexpected for the enrolled population with peripheral vascular disease and associated comorbidities.

Table 27: CEC-adjudicated Adverse Events[1] Reported in at Least 5% of Patients in Either Treatment Group Through the 24-Month Follow-up Window (AT Population)

		Randomized DCB Patients		PTA Patients	
AE Category	Event code[2]	n events	N=316 % (n patients)	n events	N=160 % (n patients)
1 Cardiac Events	1.01 Angina	24	6.6% (21)	9	5.6% (9)
2 Clinical Events	2.08 Other infection, local (req. antibiotics), specify:	33	9.8% (31)	10	5.0% (8)
	2.17 Neoplasia	18	4.4% (14)	10	5.6% (9)
	2.19 Other Clinical, specify:	55	14.2% (45)	29	12.5% (20)
	2.20 Orthopaedic Injury	16	4.1% (13)	8	5.0% (8)
	2.21 Orthopaedic Disease	19	5.4% (17)	12	6.3% (10)
	2.22 Musculoskeletal Pain	27	7.6% (24)	7	4.4% (7)
	2.25 Gastrointestinal Disorder	29	7.6% (24)	14	6.9% (11)
3 Hemorrhagic Events	3.01 Access site: Hematoma	22	6.6% (21)	5	3.1% (5)
6 Vascular Events	6.02 Restenosis of the study lesion	11	3.5% (11)	14	8.1% (13)
	6.04 Restenosis of the non-study vessel	25	7.3% (23)	10	6.3% (10)
	6.22 Target extremity pain	30	7.9% (25)	14	7.5% (12)
	6.25 Non-target extremity pain	15	4.1% (13)	9	5.6% (9)

		Randomized DCB Patients		PTA Patients	
AE Category	**Event code[2]**	**n events**	**N=316 % (n patients)**	**n events**	**N=160 % (n patients)**
	6.35 Claudication	69	17.1% (54)	48	20.6% (33)
Total	Total	726	75.9% (240)	338	68.8% (110)

[1]Includes events reported through end of 12 month window
[2] Terms were coded using a Lutonix-specific medical dictionary

5.13 Serious Adverse Events

LEVANT2 SAEs as CEC-adjudicated are summarized in Table 28. Roughly half of the subjects in each treatment group experienced at least one SAE during the study. Serious adverse events appearing to trend unfavourably for Lutonix DCB include angina, CHF, access site/vascular complications, and stroke. These are discussed further in Section 6.9 and 0 in the context of additional Lutonix DCB data from the LEVANT 2 continued access/safety registry and historic rates for the enrolled population with symptomatic PAD.

Table 28: CEC-adjudicated Serious Adverse Events Through the 24-Month Follow-up Window (AT Population)

CEC-Adjudicated SAEs through 24 Months		Randomized DCB Subjects		PTA Subjects	
			N=316		N=160
AE Category	Event code	n events	% (n subjects)	n events	% (n subjects)
1 Cardiac Events	1.01 Angina	15	4.4% (14)	3	1.9% (3)
	1.02 Atrial Fibrillation	3	0.9% (3)	2	1.3% (2)
	1.05 Other Arrhythmia, specify:	1	0.3% (1)	2	1.3% (2)
	1.06 Cardiac arrest/failure	1	0.3% (1)	0	0.0% (0)
	1.07 Hypertension (req. therapy)	1	0.3% (1)	1	0.6% (1)
	1.08 Hypotension (Sustained, req. pressors and/or IABP)	2	0.6% (2)	0	0.0% (0)
	1.09 MI: Q-wave (STEMI)	0	0.0% (0)	1	0.6% (1)
	1.10 MI: Non Q-wave (NSTEMI)	4	0.9% (3)	1	0.6% (1)
	1.11 MI: Unknown	4	1.3% (4)	2	1.3% (2)
	1.13 CHF: After discharge	9	1.9% (6)	0	0.0% (0)
	1.14 Other Cardiac, specify:	5	1.3% (4)	1	0.6% (1)

CEC-Adjudicated SAEs through 24 Months		Randomized DCB Subjects		PTA Subjects	
AE Category	Event code	n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
2 Clinical Events	2.01 Contrast media allergic reaction	1	0.3% (1)	0	0.0% (0)
	2.05 Fever, unknown etiology	1	0.3% (1)	0	0.0% (0)
	2.06 Groin infection, local (req. antibiotics)	1	0.3% (1)	0	0.0% (0)
	2.07 Skin infection, local (req. antibiotics)	2	0.6% (2)	1	0.6% (1)
	2.08 Other infection, local (req. antibiotics), specify:	6	1.9% (6)	1	0.6% (1)
	2.09 Infection, systemic (req. antibiotics)	2	0.6% (2)	1	0.6% (1)
	2.10 Renal insufficiency (> 0.5 increase in Cr from preprocedure/baseline)	3	0.9% (3)	1	0.6% (1)
	2.11 Renal failure (requiring new dialysis or prolonged hospitalization with dialysis)	0	0.0% (0)	0	0.0% (0)
	2.12 Respiratory failure: Fluid volume overload	0	0.0% (0)	0	0.0% (0)
	2.13 Respiratory failure: Exacerbation of COPD	8	1.6% (5)	1	0.6% (1)
	2.16 Pneumonia	8	2.5% (8)	2	1.3% (2)
	2.17 Neoplasia	15	3.8% (12)	9	5.0% (8)
	2.18 Pulmonary Embolism	2	0.6% (2)	0	0.0% (0)
	2.19 Other Clinical, specify:	13	3.2% (10)	6	2.5% (4)
	2.20 Orthopaedic Injury	5	1.6% (5)	4	2.5% (4)
	2.21 Orthopaedic Disease	7	1.9% (6)	5	2.5% (4)
	2.22 Musculoskeletal Pain	2	0.6% (2)	0	0.0% (0)
	2.23 Arthritis/gout	0	0.0% (0)	1	0.6% (1)
	2.24 Other Renal Events	6	0.9% (3)	0	0.0% (0)
	2.25 Gastrointestinal Disorder	6	1.9% (6)	8	4.4% (7)
	2.26 Inguinal hernia	2	0.6% (2)	0	0.0% (0)

CEC-Adjudicated SAEs through 24 Months		Randomized DCB Subjects		PTA Subjects	
AE Category	Event code	n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
	2.27 Cholelithiasis	0	0.0% (0)	1	0.6% (1)
	2.28 Benign Prostatic Hypertrophy	1	0.3% (1)	0	0.0% (0)
	2.29 Cataracts	5	1.3% (4)	3	1.3% (2)
	2.32 Electrolyte Abnormality	3	0.9% (3)	0	0.0% (0)
	2.33 Dyspnea	1	0.3% (1)	0	0.0% (0)
	2.34 Non-Cardiac Chest Pain	4	1.3% (4)	0	0.0% (0)
	2.38 Cholecystitis	1	0.3% (1)	1	0.6% (1)
3 Hemorrhagic Events	3.01 Access site: Hematoma	3	0.9% (3)	0	0.0% (0)
	3.02 Access site: Significant hemorrhage req. transfusion	4	0.9% (3)	0	0.0% (0)
	3.03 Access site: Pseudoaneurysm	4	1.3% (4)	3	1.9% (3)
	3.06 Bleeding/Hemorrhage from anticoagulants	2	0.6% (2)	0	0.0% (0)
	3.07 Bleed, Gastrointestinal	4	1.3% (4)	1	0.6% (1)
	3.09 Bleed, Retroperitoneal	2	0.6% (2)	1	0.6% (1)
	3.10 Anemia, general (req. blood transfusion)	4	0.9% (3)	1	0.6% (1)
	3.11 Other Hemorrhage, specify:	5	1.3% (4)	1	0.6% (1)
4 Neurological Events	4.01 TIA (Focal deficit resolving within 24 hours)	2	0.6% (2)	0	0.0% (0)
	4.02 Stroke (Focal deficit lasting over 24 hours)	9	2.8% (9)	1	0.6% (1)
	4.03 Other Neurologic, specify:	4	1.3% (4)	4	2.5% (4)
	4.05 Hearing loss	1	0.3% (1)	0	0.0% (0)
	4.06 syncope/near syncope/dizziness/vertigo	4	1.3% (4)	0	0.0% (0)

CEC-Adjudicated SAEs through 24 Months		Randomized DCB Subjects		PTA Subjects	
			N=316		N=160
AE Category	Event code	n events	% (n subjects)	n events	% (n subjects)
5 Angiographic Events	5.02 Target vessel injury/dissection with pre-treatment	0	0.0% (0)	0	0.0% (0)
	5.03 Target vessel injury/dissection with study treatment	6	1.9% (6)	6	3.8% (6)
	5.04 Target vessel injury/dissection with post-treatment	1	0.3% (1)	2	1.3% (2)
	5.07 Distal embolization with study treatment	1	0.3% (1)	1	0.6% (1)
	5.08 Distal embolization with post-treatment	0	0.0% (0)	1	0.6% (1)
	5.10 Arterial rupture	1	0.3% (1)	0	0.0% (0)
	5.11 Clot/Thrombus formation (thrombosis)	1	0.3% (1)	2	1.3% (2)
	5.15 Access Site Dissection	1	0.3% (1)	0	0.0% (0)
	5.17 Distal embolization (non-index procedure)	1	0.3% (1)	0	0.0% (0)

CEC-Adjudicated SAEs through 24 Months		Randomized DCB Subjects		PTA Subjects	
AE Category	Event code	n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
6 Vascular Events	6.02 Restenosis of the study lesion	5	1.6% (5)	7	3.8% (6)
	6.03 Restenosis of the study vessel	1	0.3% (1)	2	1.3% (2)
	6.04 Restenosis of the non-study vessel	24	7.0% (22)	10	6.3% (10)
	6.05 Clinically-driven target (study) lesion revascularization (TLR)	6	1.9% (6)	2	1.3% (2)
	6.06 Incidental target (study) lesion revascularization (TLR)	0	0.0% (0)	1	0.6% (1)
	6.07 Target (study) vessel revascularization (TVR)	0	0.0% (0)	0	0.0% (0)
	6.09 Target (study) extremity revascularization (non-study lesion/vessel)	0	0.0% (0)	1	0.6% (1)
	6.10 Non-target extremity revascularization	5	1.3% (4)	6	3.8% (6)
	6.11 Non-target acute limb ischemia	2	0.6% (2)	0	0.0% (0)
	6.12 Target (study) acute limb ischemia	1	0.3% (1)	0	0.0% (0)
	6.17 Non-target extremity minor/major amputation, toe(s)	0	0.0% (0)	0	0.0% (0)
	6.22 Target extremity pain	12	3.2% (10)	5	3.1% (5)
	6.24 Target extremity ischemic ulcer-New	2	0.6% (2)	0	0.0% (0)
	6.25 Non-target extremity pain	9	2.8% (9)	4	2.5% (4)
	6.27 Non-target extremity ischemic ulcer-New	0	0.0% (0)	1	0.6% (1)
	6.28 Other Vascular, specify:	2	0.6% (2)	2	1.3% (2)
	6.29 Bilateral lower extremity pain	1	0.3% (1)	3	1.9% (3)
	6.31 Deep vein thrombosis	0	0.0% (0)	0	0.0% (0)
	6.32 Non target limb aneurysm	1	0.3% (1)	0	0.0% (0)
	6.35 Claudication	50	12.3% (39)	40	16.9% (27)
7 Other Events	7.01 Other, specify:	1	0.3% (1)	0	0.0% (0)

CEC-Adjudicated SAEs through 24 Months		Randomized DCB Subjects		PTA Subjects	
AE Category	Event code	n events	N=316 % (n subjects)	n events	N=160 % (n subjects)
8 Non-Event/ Death Outcomes	8.01 Accidental death	0	0.0% (0)	1	0.6% (1)
	8.03 Cardiac death	1	0.3% (1)	0	0.0% (0)
	8.04 Sudden cardiac death	0	0.0% (0)	1	0.6% (1)
	8.06 Unknown cause of death	4	1.3% (4)	1	0.6% (1)
	8.07 Death (not otherwise specified-NOS)	0	0.0% (0)	0	0.0% (0)
	8.08 Death from neoplasia	1	0.3% (1)	0	0.0% (0)
Total	Total	338	53.5% (169)	169	50.0% (80)

5.14 Mortality

A listing of deaths reported in LEVANT 2 through the 12 month follow up window are provided in Table 29. All deaths that have been adjudicated by the CEC were adjudicated as unrelated to the device, procedure or study limb.

Through 12 months, the rate of all cause death was 2.4% (7) in the DCB group vs. 2.8% (4) in the control PTA group. Deaths were due to cardiovascular/unknown 1.6% (5) vs. 1.3% (2), cancer 0.3% (1) vs. 1.3% (2), and ischemic stroke 0.3% (1) vs. 0% (0). Mean days to death was 250 ± 124 vs. 233 ± 90 days. The median days to death were 267 for Lutonix DCB and 248.5 for control PTA. The minimum and maximum days to death for Lutonix DCB were 53 and 382 days, and 121 and 314 days for control PTA.

An additional 9 vs. 3 deaths occurred after the close of the 12 month window, 6 vs. 2 of which have not yet been CEC adjudicated, for a total reported death rate of 5.1% (16) Lutonix DCB vs. 4.4% (7) control PTA. Mean days to death was 423 ± 211 vs. 351 ± 180 days.

Table 29: LEVANT 2 Study Deaths through 12 Months

	Lutonix DCB (n=316)		Standard PTA (n=160)	
	N (%)	Time to Event Median (min, max)	N (%)	Time to Event Median (min, max)
Cancer	1 (0.3%)		2 (1.3%)	
Cardiovascular/ Unknown	5 (1.6%)		2 (1.3%)	
Ischemic Stroke	1 (0.3%)		0 (0.0%)	
TOTAL	7 (2.4%)	267.0 (53.0, 382.0)	4 (2.8%)	248.5 (121.0, 314.0)

5.15 Device usage and Malfunctions

In LEVANT 2, a total of 443 Lutonix DCBs were used to treat 336 patients randomized to the test group and 80 DCBs were used to treat 56 roll-in patients. Four Lutonix DCB device malfunctions were reported during the study.

In two of the four cases, the malfunction occurred prior to patient contact with the device. In the third case, after 37 seconds of inflation time the site noted a balloon rupture and removed the device. A second 5.0 x 100 mm LTX DCB was used to cover the remaining lesion area with no reported issues. No procedural related SAEs were reported.

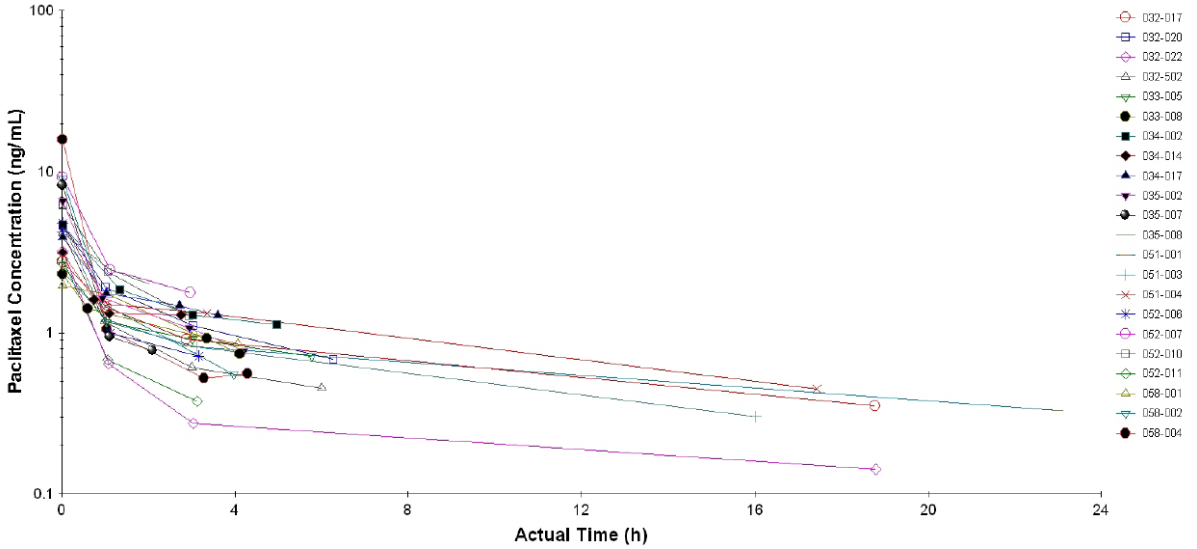
In the fourth case, the operator observed dye leaking from the balloon, and after over 50 seconds, the device was deflated and removed and a third Lutonix Catheter (6.0x 100mm) was deployed at the proximal site to treat the lesion with a final result of 20% residual stenosis. After the procedure, the patient had a grape-sized moderate-grade access site hematoma reported as an AE and underwent an additional lower extremity arterial duplex, which showed incidental findings reported as an acute, non-occlusive, severe deep vein thrombosis in the distal external iliac, common femoral, and proximal femoral veins.

5.16 Pharmacokinetic Substudy

In LEVANT 2 a pharmacokinetic sub-study was performed in a subset of 22 Lutonix DCB patients. Serum paclitaxel levels were detectable in all patients immediately post-procedure (Figure 15). Following DCB treatment, group mean values for the peak measured level (C_{max}) was 5.1 ng/mL, total area under the curve (AUC_{all}) was 8.39 ng*h/mL, and the time from start to last measurable amount (MRT_{last}) was 2.13 h, and the mean elimination half-life ($T_{½}$) was 6.88 h for evaluable patients. Serum paclitaxel concentrations drawn at 30 days were below the lower limit of detection (0.1 ng/mL) for all patients. The very low concentration and short duration of paclitaxel in the blood support the safety of Lutonix DCB

The serum paclitaxel levels measured during the LEVANT 2 pharmacokinetic sub-study are similar to those reported with treatment of the Zilver Drug Eluting Stent (single stent: C_{max} = 4.4 ng/mL; $AUC_{0\text{-}last}$ = 6.5 and $t_{1/2}$ = 2.4 h and two stents: C_{max} = 6.6 ng/mL; $AUC_{0\text{-}last}$ = 14.0 and $t_{1/2}$ = 7.0 h)[30].

Figure 15: Paclitaxel Concentration vs. Time



5.17 LEVANT 2 Subgroup Interactions

5.17.1 Analysis of Treatment Effect by Geography and Gender

Prespecified analyses were conducted to assess the potential for interaction of geography and treatment group for both primary endpoints. An interaction with geography was observed for both primary safety ($p = 0.02$) and primary efficacy ($p=0.12$) endpoints. Therefore, additional post hoc analyses have been conducted to explore the differences, to assess their potential causes and to evaluate whether or not they are clinically meaningful. The modest geographic interaction for safety and the weak interaction for efficacy are largely explained by outcome differences that are observed by gender in the two geographies (US vs. OUS). Results for females appear to account for both interactions but are driving them in opposite directions. Compared to the male cohort, the observed treatment effect favoring DCB among females was stronger with respect to safety but weaker with respect to efficacy in different geographies.

Differences in smoking status appear to be responsible for the potential interaction of both geography and gender with primary efficacy (not safety). However, the observed treatment favored control PTA solely in the non-smoking, US, female subset. Since a positive treatment effect is observed for non-smoking US males, OUS Males, and OUS females (as well as all 4 smoking subsets), it cannot be concluded that DCB is ineffective for non-smokers. The interaction for safety is explained by poor (outlier) results observed for the OUS female control PTA group.

The study was not powered to test interactions or differences between the test and control arms within regional, gender, and smoking subgroups. Therefore it is not unlikely that, by chance, different treatment effects are observed in subsets[33].

5.17.1.1 Primary Patency by Geography and Gender

The primary efficacy endpoint results for the prespecified geographic and gender subsets (shown graphically in Figure 7) above are reproduced below in Table 30. The observed treatment effect with respect to efficacy appears higher for male vs. female patients and for OUS vs. US patients. The p value was 0.12 for the prespecified interaction test with geography.

Table 30: Primary Patency at 1 Year by Geography and Gender

	Subset	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]
Geography	OUS	69.1% (67/97) [59.9, 78.3]	46.0% (23/50) [32.2, 59.8]	23.1% [6.5, 39.7]
	US	62.9% (105/167) [55.5, 70.2]	56.5% (48/85) [45.9, 67.0]	6.4% [-6.4, 19.2]
Gender	Female	56.4% (57/101) [46.8, 66.1]	61.4% (27/44) [47.0, 75.8]	-4.9% [-22.3, 12.4]
	Male	70.6% (115/163) [63.6, 77.5]	48.4% (44/91) [38.1, 58.6]	22.2% [9.8, 34.6]

To explore possible reasons for the observed differences in primary efficacy results by gender and geography, we examined what other baseline covariates might be effect modifiers, and then assessed whether a candidate effect modifier varied between sex and geography and might possibly explain the sex and geography differences. Logistic regression models are used throughout to model the odds of primary patency.

First, models exploring effect modifiers included terms for the randomized treatment group, a covariate, and the interaction of randomized treatment group with the covariate. Separate models were fit for each covariate. The list of explored covariates is taken from those prespecified in the study protocol. As shown in Table 31 below, a significant interaction with treatment group was found for smoking ($p = 0.001$) and female sex (which had been identified previously).

Table 31: Possible Treatment by Covariate Interactions for Primary Efficacy

Covariate	P-value for Interaction of Treatment Group and Covariate
ABI	0.772
Age	0.219
BMI>=30	0.577
Coronary artery disease	0.220
Diabetes	0.901
Female	0.013
Hyperlipidemia	0.460
Prior target limb intervention	0.716
Rutherford class	0.839
Smoker (current)	***0.001***
Stenosis	0.287
Target lesion length	0.825

The prevalence of smoking varied significantly by geography (Table 32) and by gender (Table 33) and therefore may explain the observed differences in treatment effect between gender and geography.

Table 32: Smoking Status by Geography

Variable	US	EU	P-value
Smoking, % (n/N)			<0.001
Current smoker	30.2% (91/301)	42.3% (74/175)	
Never smoked	17.6% (53/301)	23.4% (41/175)	
Previously smoked	52.2% (157/301)	34.3% (60/175)	

Table 33: Smoking Status by Gender

Variable	Female	Male	P-value
Smoking, % (n/N)			<0.001
Current smoker	27.8% (49/176)	38.7% (116/300)	
Never smoked	34.1% (60/176)	11.3% (34/300)	
Previously smoked	38.1% (67/176)	50.0% (150/300)	

A series of exploratory statistical models were investigated (Table 34) to further examine the interrelationships between gender, geography, and smoking. In a model with only main effects, treatment and smoking are significant but gender and geography are not. Furthermore, with multivariable stepwise selection including all possible interactions of treatment, sex, geography, and smoking, the final model retained only terms for treatment, smoking, and the interaction of treatment and smoking. Each of these models indicates that smoking is the better statistical predictor of outcome (compared to sex or geography).

Table 34: Exploratory Statistical Models for Gender, Geography, and Smoking

Statistical Model	Terms	P-values
Multivariable; main effects only	Treatment Sex Geography Smoking	0.017 0.369 0.796 0.037
Multivariable; main effects for treatment, sex, geography, smoking; interaction of smoking with treatment	Treatment Sex Geography Smoking Treatment x smoking	0.865 0.408 0.589 0.246 0.001
Multivariable stepwise selection, including all possible interactions of treatment, sex, geography, and smoking. The final model retained only terms for treatment, smoking, and the interaction of treatment and smoking.	Treatment Smoking Treatment x smoking	0.884 0.243 0.001

Primary Efficacy results are presented by smoking status in Table 35 and Table 36. A large difference in favor of test DCB is observed for current smokers as compared to previous or never smokers.

Table 35: Primary Efficacy Endpoint at 12 Months by Smoking Status (Current vs. Previous or Never)

Measure	Smoking Status	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]
Primary Patency[1]	Current	79.6% (74/93) [71.4, 87.8]	43.9% (18/41) [28.7, 59.1]	35.7% [18.4, 52.9]
	Previous or never	57.3% (98/171) [49.9, 64.7]	56.4% (53/94) [46.4, 66.4]	0.9% [-11.5, 13.4]

Differences in baseline characteristics by smoking status were explored. Compared to nonsmokers, current smokers were younger (64 vs. 71, $p < 0.001$), more often male (70% vs. 59%, $p = 0.017$), of Caucasian race (94% vs. 86%, $p = 0.040$), and taller (172 vs. 168 cm, $p < 0.001$). Current smokers had less dyslipidemia (83% vs. 91%, $p = 0.007$), diabetes (29% vs. 50%, $p < 0.001$), and coronary artery disease (40% vs. 54%, $p = 0.004$). Current smokers had fewer severely calcified lesions (5.5% vs. 12%, $p = 0.024$) and better run-off (2.2 vs. 1.9 vessels, $p < 0.001$), but more total occlusions (27% vs. 18%, $p = 0.015$). Of these characteristics, smoking is the best statistical predictor of outcomes.

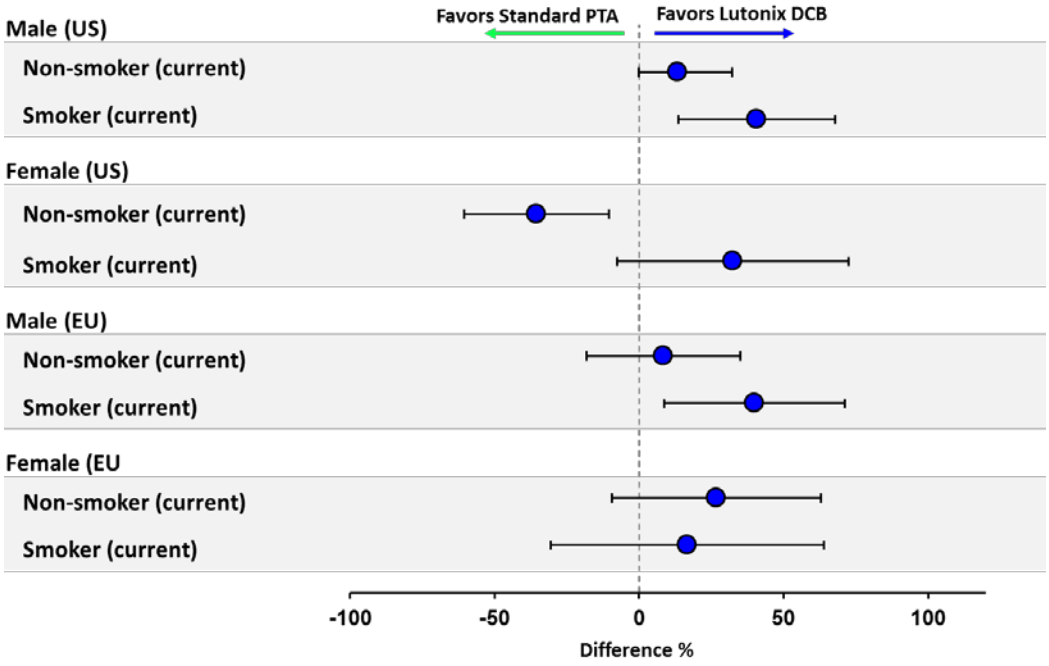
As shown in Table 36 and Figure 16, a positive treatment effect in favor of Lutonix DCB is observed for non-smoking US male, OUS male, and OUS female subsets. Therefore, it cannot be concluded that Lutonix DCB is ineffective for non-smokers. The treatment effect favors Lutonix DCB in 7 of the 8 smoking/geography/subgroups by differences between 8.4% and 40.7%. Only for non-smoking US females does the treatment difference (-35.4%) favor control PTA.

Table 36: Primary Efficacy Endpoint at 12 Months by Smoking, Gender, and Geography

		US			OUS		
Gender	Smoking Status	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference[2] % [95% CI]	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference[2] % [95% CI]
Male	Non-smoker (current)	67.2% (45/67) [55.9, 78.4]	53.8% (21/39) [38.2, 69.5]	13.3% [-5.7, 32.3]	56.3% (18/32) [39.1, 73.4]	47.8% (11/23) [27.4, 68.2]	8.4% [-18.3, 35.1]
	Smoker (current)	82.8% (24/29) [69.0, 96.5]	42.1% (8/19) [19.9, 64.3]	40.7% [13.5, 67.8]	80.0% (28/35) [66.7, 93.3]	40.0% (4/10) [9.6, 70.4]	40.0% [8.8, 71.2]

		US			OUS		
Gender	**Smoking Status**	**Test DCB %(n/N) [95% CI]**	**Control PTA %(n/N) [95% CI]**	**Difference[2] % [95% CI]**	**Test DCB %(n/N) [95% CI]**	**Control PTA %(n/N) [95% CI]**	**Difference[2] % [95% CI]**
Female	Non-smoker (current)	40.7% (22/54) [27.6, 53.8]	76.2% (16/21) [58.0, 94.4]	-35.4% [-60.6, -10.3]	72.2% (13/18) [51.5, 92.9]	45.5% (5/11) [16.0, 74.9]	26.8% [-9.4, 63.0]
	Smoker (current)	82.4% (14/17) [64.2, 100.0]	50.0% (3/6) [10.0, 90.0]	32.4% [-7.7, 72.4]	66.7% (8/12) [40.0, 93.3]	50.0% (3/6) [10.0, 90.0]	16.7% [-30.7, 64.0]

Figure 16: Primary Efficacy Endpoint at 12 Months by Smoking, Gender, and Geography



Significant differences in baseline characteristics between randomized treatment groups were observed within the US female non-smoking (but not the smoking) subset that confound interpretation of outcomes for that subset taken alone. Among non-smoking US females, patients allocated to Lutonix DCB compared to control PTA had smaller vessels (RVD 4.3 vs. 4.8 mm, $p < 0.001$), a higher site-reported dissection rate after treatment with the randomized study device (45.3% vs. 22.2%, $p = 0.039$) with a lower rate of bailout stenting (0.0% vs. 7.4%, $p = 0.028$), and the final post-procedural minimal lumen diameter (MLD) was 3.5 vs. 3.8 mm, $p = 0.016$. There were also (non-significantly) more TASC C (2 vs. 0) and popliteal lesions treated (11 vs. 2). Over time, the same amount of late lumen loss results in higher percent diameter stenosis for smaller lumen diameters. All of these chance differences in lesion allocation and procedural results would be expected to favor primary patency outcomes for the lesions treated in the control PTA group.

With respect to risk-benefit, it is interesting to note that even though the largest positive effect for primary efficacy was observed for current smokers, the largest positive effect for primary safety was observed for never-smokers, as shown in Table 37.

.

Table 37: Primary Safety Endpoint Success Rate at 12 Months by Smoking Status

Measure	Smoking Status	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]
Freedom from Primary Safety Event[1]	Current smoker	86.1% (87/101) [79.4, 92.9]	78.3% (36/46) [66.3, 90.2]	7.9% [-4.6, 20.4]
	Never smoked	87.3% (48/55) [78.5, 96.1]	68.2% (15/22) [48.7, 87.6]	19.1% [0.5, 37.7]
	Previously smoked	80.8% (105/130) [74.0, 87.5]	82.7% (62/75) [74.1, 91.2]	-1.9% [-12.6, 8.8]

Overall, the variation in treatment effect by geography and gender is driven by an outlier result for the non-smoking US female population. Although randomization successfully balanced baseline characteristics for the ITT population, within that subgroup there were significant differences favoring expected outcomes for control PTA. The most likely explanation for these findings is chance, and these observations do not impact interpretation of the positive primary endpoint results observed for the ITT population.

5.17.1.2 Primary Safety by Geography and Gender

The primary safety endpoint results for the prespecified geographic and gender subsets (illustrated in Figure 8 above) are reproduced below in Table 38 below. The treatment effect with respect to safety appears higher for female vs. male patients and for OUS vs. US patients. The p-value for the prespecified interaction test with geography was 0.02.

Table 38: Primary Safety Endpoint Success Rate at 1 Year by Geography and Gender

	Subset	Test DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]	Difference % [95% CI]
Geography	OUS	88.7% (94/106) [82.6, 94.7]	71.7% (38/53) [59.6, 83.8]	17.0% [4.8, 29.2]
	US	81.1% (146/180) [75.4, 86.8]	83.3% (75/90) [75.6, 91.0]	-2.2% [-11.6, 7.2]
Gender	Female	80.4% (90/112) [73.0, 87.7]	67.4% (31/46) [53.8, 80.9]	13.0% [-1.2, 27.1]
	Male	86.2% (150/174) [81.1, 91.3]	84.5% (82/97) [77.3, 91.7]	1.7% [-6.8, 10.1]

To explore possible reasons for the sex and geography differences for primary safety, a post hoc analysis was performed to determine if any other baseline covariates might be an effect modifier. Logistic regression models exploring effect modifiers included terms for the randomized treatment

group, a covariate, and the interaction of randomized treatment group with the covariate. Separate models were fit for each covariate prespecified in the study protocol. As shown in Table 39, no covariate explored as an effect modifier had a p-value that approached a significance level of 0.05. The smallest observed p-value was for gender, with a p-value of 0.302.

Table 39: Treatment by Covariate Interactions for Primary Safety

Covariate	P-value for Interaction of Treatment Group and Covariate
ABI	0.986
Age	0.579
BMI>=30	0.575
Coronary artery disease	0.303
Diabetes	0.664
Female	0.302
Hyperlipidemia	0.970
Prior target limb intervention	0.709
Rutherford class	0.676
Smoker (current)	0.555
Stenosis	0.990
Target lesion length	0.968

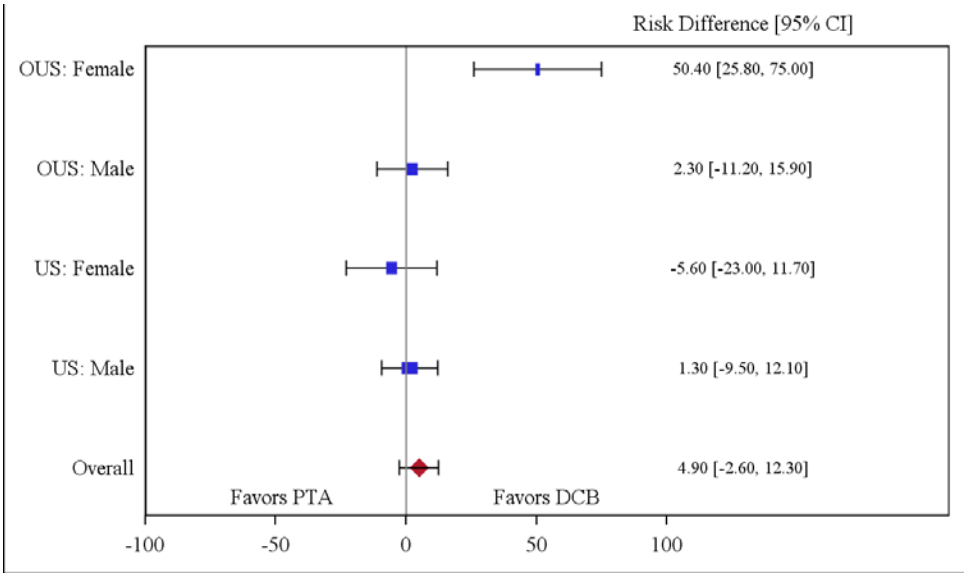
Results for primary safety endpoint success rates by gender by geography are provided in Table 40. This table shows that the safety result variation by geography is driven by gender, primarily by very low success rates for control PTA females outside the US. The post-hoc three way interaction of treatment group, gender, and geography for the primary safety endpoint was statistically significant, p=0.010. There were a total of 16 females outside the US in the control PTA group, which limits the potential for further exploratory analyses.

Table 40: Composite Safety Success Rates at 1 year by Gender by Geography (ITT Population)

	US			OUS		
Gender	**Test DCB %(n/N) [95% CI]**	**Control PTA %(n/N) [95% CI]**	**Difference % [95% CI]**	**Test DCB %(n/N) [95% CI]**	**Control PTA %(n/N) [95% CI]**	**Difference % [95% CI]**
Female	74.4% (58/78) [64.7, 84.0]	80.0% (24/30) [65.7, 94.3]	-5.6% [-23.0, 11.7]	94.1% (32/34) [86.2, 100.0]	43.8% (7/16) [19.4, 68.1]	50.4% [25.8, 75.0]
Male	86.3% (88/102) [79.6, 93.0]	85.0% (51/60) [76.0, 94.0]	1.3% [-9.5, 12.1]	86.1% (62/72) [78.1, 94.1]	83.8% (31/37) [71.9, 95.7]	2.3% [-11.2, 15.9]

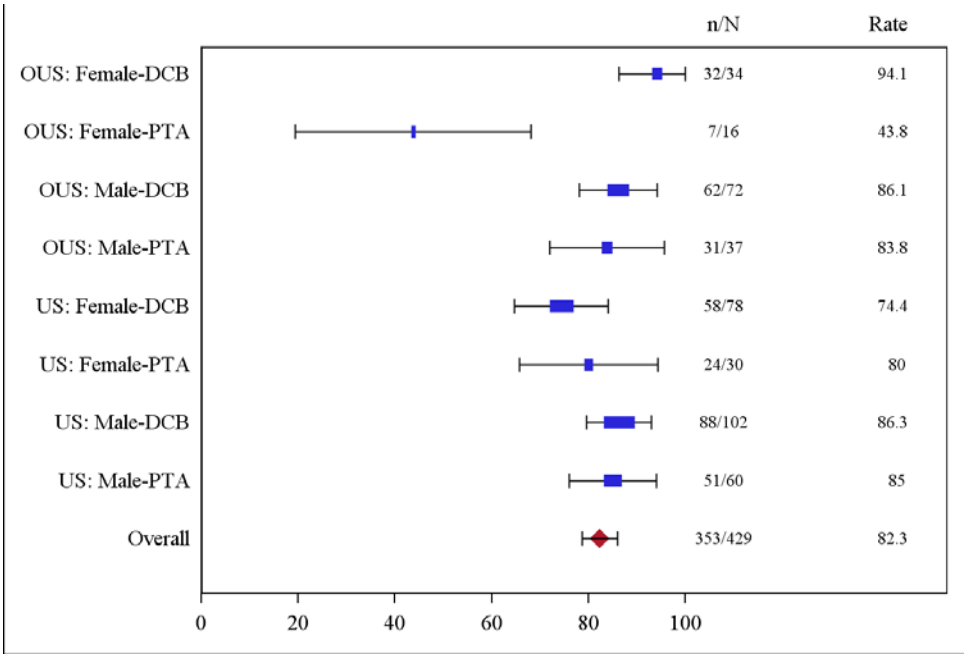
These results are shown graphically in forest plots for both treatment effect (Figure 17) and for the absolute observed rates in each group (Figure 18). The risk difference in OUS females is 50.4%, while the observed risk difference in US females is -5.6%. Of the 4 gender/geography subgroups, 3 subgroups favor Lutonix DCB. Importantly, the difference in non-US females is driven primarily by the control arm, in which only a 43.8% safety endpoint success rate was observed, in contrast to the success rate of 74.4 to 94.1% observed for all other test and control cohorts.

Figure 17: Risk Difference in Primary Safety Rate by Gender by Region



Length of box for risk difference estimate is proportional to the relative size of the subgroup. CIs are calculated using Farrington-Manning methods for the primary safety endpoint.

Figure 18: Primary Safety Rate by Gender by Region



Length of box for risk difference estimate is proportional to the relative size of the subgroup. CIs are calculated using Farrington-Manning methods for the primary safety endpoint.

Although the female OUS control population had the lowest safety endpoint success rate, the female OUS test DCB population had the highest safety rate. No demographic or procedural differences between test and control groups were observed for the OUS female population that might account for this difference. The only significantly different risk factor among OUS females places the test DCB cohort at higher risk than the control PTA cohort (92.1% vs. 66.7% hypercholesterolemia, p = 0.015).

The female cohort enrolled OUS did not appear to reflect a population at higher safety risk than the US female cohort. There were no significant differences in any of the covariates that were associated with safety endpoint failure in the ITT population. The control arm of the OUS female cohort would have been expected to have no more safety events than the control arm of the US female cohort based on baseline characteristics.

In summary, the modest interaction observed for the primary safety endpoint is driven by the control arm of one gender/geographic subset: control OUS females did very poorly compared to test DCB OUS females (and all other cohorts). A trend towards a benefit in safety for the Lutonix DCB was observed for both the US and OUS male cohorts. Three of the four post hoc gender/geography subsets trended favorably for Lutonix DCB over control, and the study was not powered to assess safety within subsets. Given the small sample sizes and the lack of any explanatory clinical difference between US and OUS females, chance cannot be ruled out as an explanation for the observed interaction. The overall safety results and results within the US provide reasonable assurance of safety to support US approval.

5.17.2 Analysis of Treatment Effect by Investigative Site

Evaluation of the variation in treatment effect for both primary patency and composite safety were also examined by investigative site. As shown in Table 41, the prespecified statistical analysis of interaction by investigative site yielded some evidence for interaction for primary patency (p value for interaction = p=0.03) but not for the composite safety endpoint (p value for interaction = p=0.31). A review of baseline disease characteristics and covariates did not show evidence that the potential interaction for primary patency may be caused by such differences among sites.

The prespecified test was based on a mixed effects model that includes random effects for site and for the interaction of treatment group and site; this tests for variation between sites assuming that the variation should be random rather than attributable to fixed characteristics at sites. With only one degree of freedom, this model does not take into account the large number of sites. Most clinical trials examine site variation based upon classifying investigative site as a fixed effect since sites are not randomly selected from all possible sites and clinical outcomes do not necessarily occur randomly across sites. Post hoc testing for interaction when using a fixed effects model found an interaction p value > 0.97 for both primary safety and primary efficacy endpoints (Table 41).

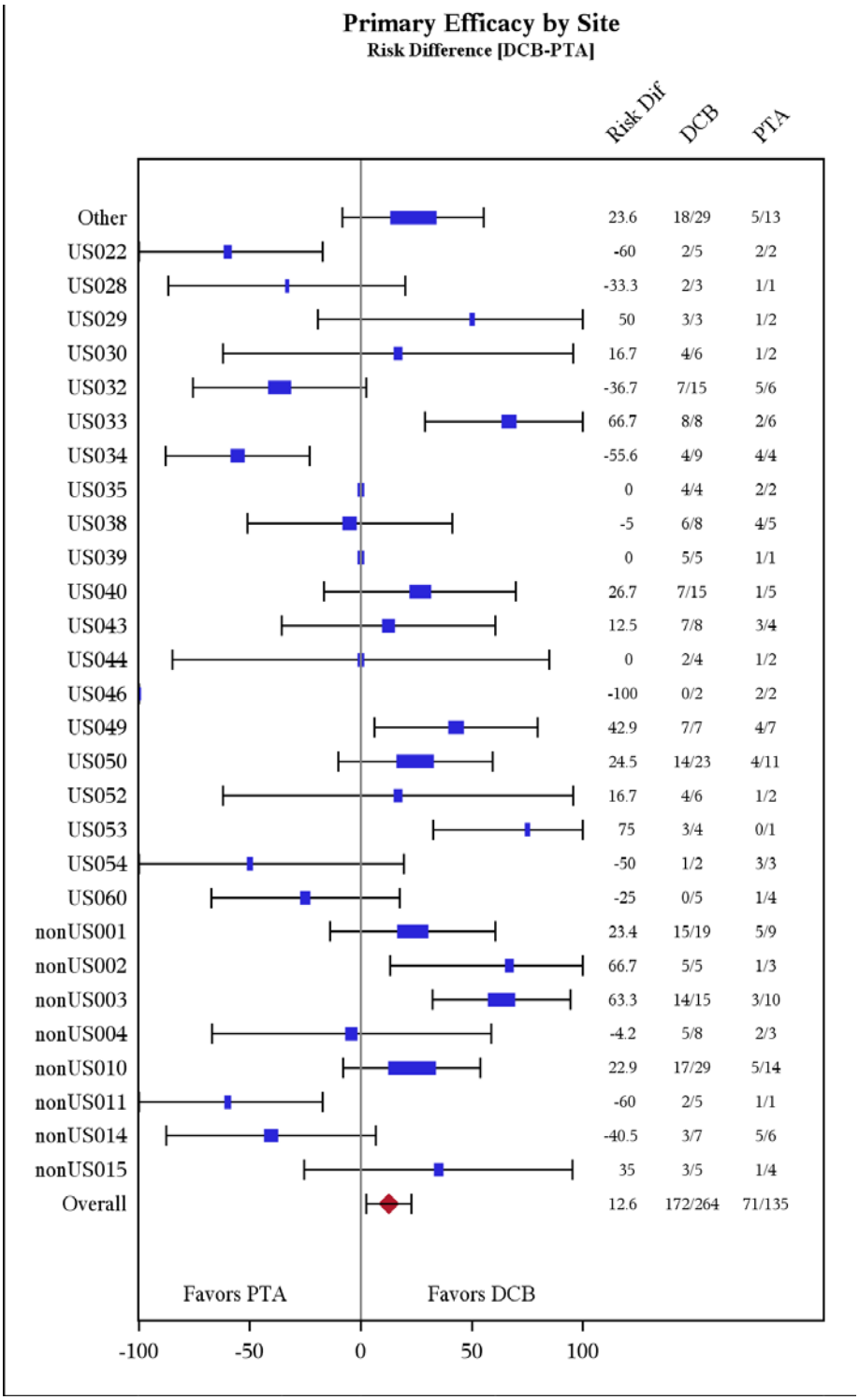
Table 41: Model Dependency of Site Interaction

Criteria	Random Effects P-value[3]	Fixed Effects P-value[4]
Primary Safety Event[1]	0.3141	0.9998
Primary Patency Failure[2]	0.0300	0.9753

[1] Composite of failure from all-cause perioperative (≤30 day) death, index limb amputation (above or below the ankle), index limb re-intervention, or index-limb-related death. For safety, sites with 10 or fewer randomized subjects with endpoint results were combined.
[2] Primary Patency failure is defined as the presence of target lesion restenosis (defined by core lab adjudication) or target lesion revascularization (TLR). For patency, sites with 3 or fewer randomized subjects with endpoint results were combined.
[3] For interaction term variance component from a mixed effects logistic regression model with random effects for site and interaction of site and treatment group and fixed effect for treatment (prespecified)
[4] For interaction term variance component from a fixed effects logistic regression model (post-hoc)

Figure 19 provides a forest plot of primary patency by investigative site and demonstrates that the treatment effect was not dependent upon one or even a few sites in either the US or EU. Variability is observed, but this is expected given the small number of subjects enrolled at many sites. The treatment effect favored DCB in 13 of 19 sites that had more than 8 evaluable subjects and in 6 of 7 sites that had more than 20 or more subjects. The distribution of effect sizes among sites appears random, and the treatment effect favors DCB at most sites, particularly at those with highest enrollment, in both US and OUS geographies. Overall, there is no evidence that the treatment depends upon site, and the findings are consistent with a positive treatment effect from DCB. Notwithstanding the interaction observed with the prespecified mixed effects model, these data suggest poolability of clinical sites.

Figure 19: Difference between Test and Control Primary Patency Rates by Site



Length of box for risk difference estimate is proportional to the relative size of the subgroup.
CIs are calculated using Wald methods.

6 LEVANT 2 Continued Access Registry and Combined Lutonix DCB Safety Analysis

6.1 Summary

- Enrollment of 657 single arm Lutonix DCB patients at 63 sites completed September 2013.
- Inclusion/exclusion criteria, treatment protocol, and follow-up schedule identical to the LEVANT 2 RCT.
- Baseline characteristics and treated lesions were similar to the randomized cohort.
- Follow-up visits have been completed for 649 patients (99%) at 30 days, 541 patients (82%) at 6 months, and 227 patients (35%) at 12 months.
- Follow-up and CEC Adjudications are ongoing.
- No unexpected adverse events were observed, and no new safety risks were identified.
- In the combined safety analysis (including the roll-in and randomized patients), 1029 patients have been treated with the Lutonix DCB and followed for a median of 341 days.

6.2 Primary Objective

The primary objective of the study was to assess safety and efficacy of use of Lutonix DCB for treatment of stenosis of the femoropopliteal arteries in a large population of subjects.

6.3 Study Overview

This single-arm follow-on to the LEVANT 2 RCT was designed to collect additional safety and efficacy information on the Lutonix DCB for treatment of stenosis or occlusion of the femoropopliteal arteries in a larger patient population. The study protocol mimicked the LEVANT 2 randomized investigational plan, except that all patients were treated with Lutonix DCB instead of being randomized. Inclusion and exclusion criteria, study device, treatment, follow-up schedule and definitions are all identical.

Sites that participated in the randomized portion of LEVANT 2 study and an additional 24 sites enrolled under identical protocols (Continued Access and Safety Registry).

6.4 Endpoints and Statistical Analysis

The primary endpoint is the rate of unanticipated device- or drug- related adverse events over time through 60 months. Secondary endpoints include the primary and secondary endpoints of the LEVANT 2 randomized trial.

Endpoints are analyzed according to the methods of the LEVANT 2 randomized study. Together with the roll-in and randomized-to-Lutonix DCB patients in the randomized study, a sample size of 650 additional single arm DCB subjects would provide a safety dataset on 1022 treated subjects. Allowing for up to 15% loss-to-follow-up, the evaluable sample size of 869 test subjects provides ability to detect and describe the rate of rare unanticipated adverse events with some precision. If the observed rare adverse event rate is 1%, then the upper limit of the 95% CI is 1.8%. Assuming an expected 1% incidence rate, Power is > 95% to observe at least 4 unexpected SAEs. Similarly, if the observed rate is 2%, then the upper limit of the 95% CI is 3.0%. Assuming an expected 2% incidence rate, Power is > 95% to observe at least 11 unexpected SAEs.

All data are analyzed and reported for each Lutonix DCB cohort separately and for the all DCB-treated cohort pooled.

6.5 Enrollment and Follow-up

Enrollment began on June 19, 2012 and was completed on September 27, 2013. A total of 657 subjects were enrolled at 63 sites across the United States (US) and Europe (EU).

Disposition of all DCB-treated patients in the LEVANT 2 studies is shown separately and together in Table 42 (with percentages based on a denominator of all enrolled patients ITT, not non-exited patients). As of the database export on February 26, 2014, in the continued access/safety cohort (CA) the 30-day follow-up window has been completed (99% visit compliance), and approximately 82% and 35% of subjects has completed 6-month and 12 month follow-up, respectively. For the combined All DCB-treated cohort of 1029 patients, 99% have had 30-day visits, 84% had 6 month visits, and 52% have had 12 month visits. Median time from enrolment to last visit is 341 days (Table 43)

Table 42: Disposition by Visit Window for All Lutonix DCB Cohorts

Visit Interval	Disposition	Roll-in % (n/N)	Randomized DCB % (n/N)	Continued Access % (n/N)	All DCB % (n/N)
1 Month	Exited	0.0% (0/56)	0.3% (1/316)	0.8% (5/657)	0.6% (6/1029)
	Had visit	98.2% (55/56)	99.1% (313/316)	98.8% (649/657)	98.8% (1017/1029)
6 Months	Exited	8.9% (5/56)	4.1% (13/316)	1.2% (8/657)	2.5% (26/1029)
	Had visit	92.9% (52/56)	92.7% (293/316)	82.3% (541/657)	84.4% (868/1029)
12 Months	Exited	5.4% (3/56)	4.1% (13/316)	0.9% (6/657)	2.1% (22/1029)
	Had visit	82.1% (46/56)	88.6% (280/316)	34.6% (227/657)	51.6% (531/1029)

Table 43: Time from Index Procedure to Last Follow-up for All Lutonix DCB Cohorts

Days in Study[1]	Randomized DCB	Randomized PTA	Roll-in DCB	CA Registry DCB	All DCB Subjects
Mean ± SD (N) (Min, Max) 25th, 50th, and 75th percentiles	478.0 ± 214.3 (314) (17, 887) 357, 386, 700	489.8 ± 219.9 (158) (20, 800) 351, 399, 700	534.5 ± 253.3 (56) (20, 872) 362, 690, 737	224.0 ± 121.0 (650) (17, 525) 166, 191, 358	319.2 ± 207.3 (1020) (17, 887) 179, 341, 382

[1]Summaries only include subjects with at least one follow-up visit (9 subjects had none).

6.6 Demographics and Baseline Characteristics

Baseline demographics, cardiac medications, clinical characteristics, and treated lesions were generally similar for all Lutonix DCB cohorts. All three cohorts were comparable with respect to number of lesions treated, lesion length, diameter of stenosis, lesion class, percent occlusion, location, and other lesion-specific and procedural measures.

Overall, Lutonix DCB-treated cohorts were also representative of the general population with peripheral arterial disease (PAD). Baseline characteristics that were also reported for the cohort with established PAD in the > 65,000 patient multinational REACH registry [31, 34] are provided in Table 44 below.

Table 44: Select Baseline Characteristics of all Lutonix DCB Cohorts and the PAD cohort of REACH

Variable	Roll-in DCB (n=56)	RCT DCB (n=316)	CA DCB (n=657)	All LEVANT2 DCB (n=1029)	REACH Registry (Bhatt 2006) Established PAD Cohort (n = 8273)
Age (years), Mean ± SD	69.2 ± 9.6	67.8 ± 10.0	68.7 ± 9.5	68.4 ± 9.7	69.2 ± 9.2
Male Gender, % (n/N)	60.7%	61.1%	63.8%	62.8%	70.7%
Diabetes Mellitus, % (n/N)	42.9%	43.4%	36.7%	39.1%	44.2%
Hypertension, % (n/N)	85.7%	89.2%	88.0%	88.2%	81.0%
Dyslipidemia/Hypercholesterolemia, % (n/N)	82.1%	89.6%	83.7%	85.4%	66.7%
Obesity (BMI>=30), % (n/N)	35.7%	34.8%	29.7%	31.6%	23.8%
Smoking, Current % (n/N)	30.4%	35.1%	35.8%	35.3%	24.5%
Smoking, Previous % (n/N)	53.6%	44.0%	45.8%	45.7%	50.9%
Previous CAD, % (n/N)	51.8%	49.7%	48.7%	49.2%	51.9%

6.7 Results

In the continued access (CA) study, 894 devices were deployed in 657 patients. Device success was 100% and procedural success was 88%. There were 4 reported device malfunctions (all of which occurred outside the body).

No unanticipated device- or drug-related adverse events have been observed (the primary endpoint).

This interim summary is focused on the cumulative safety experience of Lutonix DCB. However, interim registry results for the primary endpoints of the Levant 2 randomized study are comparable. At 6 and 12 months, respectively, 66% and 29% of continued access patients are evaluable for primary patency and 83% and 35% are evaluable for composite safety. At 6 and 12 months, respectively, the observed primary patency rate is 90.1% and 71.7% and the composite safety rate is 99.5% and 99.1% for the CA cohort by Kaplan-Meier analysis.

6.7.1 Primary Patency – Continued Access Registry

Primary patency is defined as the absence of binary restenosis (as adjudicated by the blinded core-lab) and freedom from target lesion revascularization (TLR, adjudicated by the CEC).

The proportion of subjects with primary patency at 6 months and 12 months is presented in Table 45. Primary patency was observed in 81.4% of subjects at 6 months and in 47.2% at 12 months from the continued access cohort evaluable at the time of this report.

Please note that the apparently low patency success rate reported in Table 45 below for the continued access cohort is an artifact of missing data. All prior failures are included as evaluable at 12 months, while success requires valid DUS obtained after the 12 month follow-up window opens. Since most patients have not had 12 month follow-up, prior (all 6 month) failures are concentrated in the evaluable cohort while successes are missing.

Table 45: Primary Patency of Lutonix DCB at 6 Months and 12 Months

Study	Time Point	Failure Patients	Success Patients	Evaluable Patients	Patency Success Rate (%)
LEVANT 2 Randomized DCB	6 m	52	225	277	81.2% [76.6, 85.8]
	12 m	92	172	264	65.2% [59.4, 70.9]
LEVANT 2 CA/Safety Registry DCB	6 m	81	354	435	81.4% [77.7, 85.0]
	12 m	102	91	193	47.2% [40.1, 54.2]

[1] Primary Patency is defined as freedom from target lesion restenosis (defined by core lab adjudication) and target lesion revascularization (TLR).
[2] Based on asymptotic Likelihood Ratio test. CIs for groups and difference are asymptotic.

Primary patency results between 1 and 6 months for the Continued Access cohort are identical to those observed for randomized DCB (81.2% vs. 81.4%). As shown in Table 46 below, there have been only 21 additional patency failures between 6 and 12 month visit windows in the continued access cohort. The primary patency rate among subjects that have not had a failure before the close of the 6 month visit window that are evaluable at 12 months (n=212 in the Randomized Study and n = 112 in the Continued Access Registry) are identical for randomized and continued access DCB cohorts (81.1% vs. 81.3%). Given the interim status of the analysis with very limited 12 month follow-up for the continued access, the comparison of primary patency rates by visit window (rather than cumulative) is more appropriate, as shown by Table 46 below. Observed results of the two studies are indistinguishable.

Table 46: Non-Cumulative Primary Patency Rates by Visit Window (LEVANT 2 Randomized DCB vs. Continued Access/Safety DCB).

Study	Patency Failures by Visit Window		Patency Success Rate within Visit Window Only (excluding prior 6m failures)	
	Window	In-Window Failures Patients (n)	In-Window Evaluable Patients Only (n)	Adjusted Patency Success Rate (%)
Randomized DCB	0-6 months	52	277	81.2%
	6-12 months	40*	212**	81.1%
CA/Safety Registry DCB	0-6 months	81	435	81.4%
	6-12 months	21*	112**	81.3%

* With removal of prior 6m failures patients (i.e. 92-52 = 40 for pivotal study; 102 -81 = 21 for safety registry)
** With removal of prior 6m failure patients (i.e. 264-52 = 212 for pivotal study; 193-81=112 for safety registry)

The results by visit window are consistent with the Kaplan Meier analysis shown below which handles the large amount of missing data better than the interim proportion based analysis. Primary patency for the randomized DCB cohort is 88.8% at 183 days and 73.5% at 365 days by Kaplan Meier. Similarly, primary patency for the Continued Access/Safety registry is 90.1% at 183 days and 71.7% at 365 days by Kaplan Meier analysis.

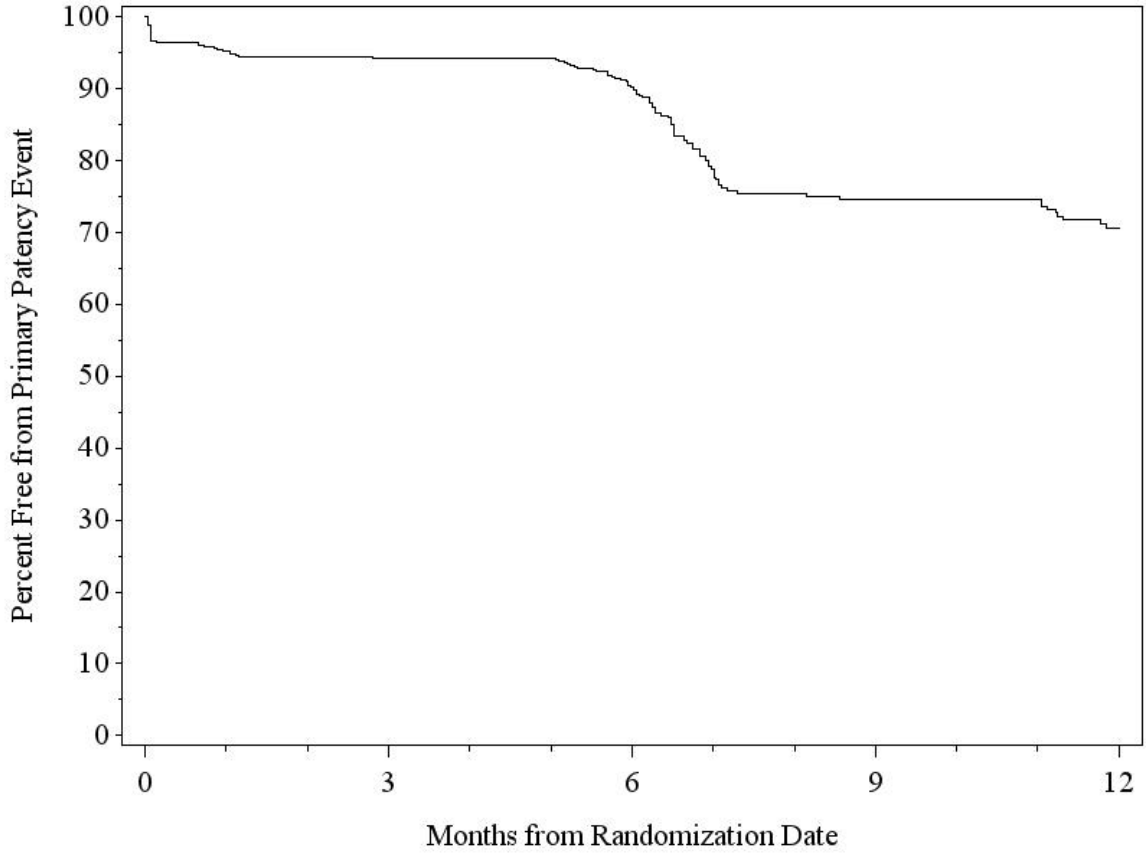
Based on interim analysis, the primary patency rate observed for the Continued Access registry is identical to the rate observed for the randomized DCB cohort, and the apparently lower patency rate at 12 months is an artifact of the small denominator with most 12 months visits still pending.

Table 47: Primary Patency Rate by Kaplan-Meier Analysis (Continued Access DCB Population)

Month[1]	Survival %[95% CI]	Subjects with Event	Censored Subjects	Subjects at Risk
1 month	95.4% [93.5, 96.7]	30	37	590
6 months	90.1% [87.2, 92.3]	57	214	386
12 months	71.7% [66.5, 76.2]	113	438	106

[1] Primary Patency success is defined as the absence of target lesion restenosis (defined by core lab adjudication) and freedom from target lesion revascularization (TLR).

Figure 20: Kaplan-Meier Graph of Primary Patency (Continued Access DCB Population)



6.7.2 Secondary Safety Endpoints

Secondary safety endpoints by time point are generally comparable to those of the randomized cohort (Table 48). The first row includes Continued Access results for the primary safety endpoint of the Levant 2 Randomized study, and based on interim data, point estimates for composite safety are higher for the entire Lutonix DCB-treated population than observed in the randomized study. These data should be interpreted with caution given ongoing adjudications and limited long term follow-up.

Table 48: Secondary Safety Endpoints by Time Point for All DCB Cohorts

Outcome	Visit	Roll-in DCB %(n/N) [95% CI] [2]	Randomized DCB %(n/N) [95% CI] [2]	Continued Access %(n/N) [95% CI] [2]	All DCB %(n/N) [95% CI] [2]
Freedom from Primary Safety Event[1]	1 Month	100.0% (54/54) [100.0, 100.0]	99.4% (306/308) [98.5, 100.0]	99.7% (621/623) [99.2, 100.0]	99.6% (981/985) [99.2, 100.0]
	6 Months	96.1% (49/51) [90.8, 100.0]	92.0% (275/299) [88.9, 95.1]	99.3% (542/546) [98.6, 100.0]	96.7% (866/896) [95.5, 97.8]
	12 Months	91.5% (43/47) [83.5, 99.5]	83.9% (240/286) [79.7, 88.2]	98.2% (224/228) [96.5, 99.9]	90.4% (507/561) [87.9, 92.8]
Death[3]	1 Month	0.0% (0/54) [0.0, 0.0]	0.0% (0/308) [0.0, 0.0]	0.2% (1/623) [0.0, 0.5]	0.1% (1/985) [0.0, 0.3]
	6 Months	3.8% (2/53) [0.0, 8.9]	0.7% (2/301) [0.0, 1.6]	0.2% (1/546) [0.0, 0.5]	0.6% (5/900) [0.1, 1.0]
	12 Months	6.1% (3/49) [0.0, 12.8]	2.4% (7/290) [0.6, 4.2]	0.4% (1/228) [0.0, 1.3]	1.9% (11/567) [0.8, 3.1]
Major Amputation	1 Month	0.0% (0/54) [0.0, 0.0]	0.0% (0/308) [0.0, 0.0]	0.0% (0/622) [0.0, 0.0]	0.0% (0/984) [0.0, 0.0]
	6 Months	0.0% (0/51) [0.0, 0.0]	0.3% (1/299) [0.0, 1.0]	0.0% (0/545) [0.0, 0.0]	0.1% (1/895) [0.0, 0.3]
	12 Months	0.0% (0/47) [0.0, 0.0]	0.3% (1/286) [0.0, 1.0]	0.0% (0/227) [0.0, 0.0]	0.2% (1/560) [0.0, 0.5]
Minor Amputation	1 Month	0.0% (0/54) [0.0, 0.0]	0.0% (0/308) [0.0, 0.0]	0.0% (0/622) [0.0, 0.0]	0.0% (0/984) [0.0, 0.0]
	6 Months	0.0% (0/51) [0.0, 0.0]	0.0% (0/298) [0.0, 0.0]	0.0% (0/545) [0.0, 0.0]	0.0% (0/894) [0.0, 0.0]
	12 Months	0.0% (0/47) [0.0, 0.0]	0.0% (0/285) [0.0, 0.0]	0.0% (0/227) [0.0, 0.0]	0.0% (0/559) [0.0, 0.0]

Outcome	Visit	Roll-in DCB %(n/N) [95% CI] [2]	Randomized DCB %(n/N) [95% CI] [2]	Continued Access %(n/N) [95% CI] [2]	All DCB %(n/N) [95% CI] [2]
Amputation-Free Survival (AFS)	1 Month	100.0% (54/54) [100.0, 100.0]	100.0% (308/308) [100.0, 100.0]	99.8% (622/623) [99.5, 100.0]	99.9% (984/985) [99.7, 100.0]
	6 Months	96.2% (51/53) [91.1, 100.0]	99.3% (298/300) [98.4, 100.0]	99.8% (545/546) [99.5, 100.0]	99.4% (894/899) [99.0, 99.9]
	12 Months	93.9% (46/49) [87.2, 100.0]	97.6% (283/290) [95.8, 99.4]	99.6% (227/228) [98.7, 100.0]	98.1% (556/567) [96.9, 99.2]
Total TVR	1 Month	0.0% (0/54) [0.0, 0.0]	0.3% (1/308) [0.0, 1.0]	0.2% (1/622) [0.0, 0.5]	0.2% (2/984) [0.0, 0.5]
	6 Months	3.9% (2/51) [0.0, 9.2]	6.7% (20/298) [3.9, 9.6]	0.6% (3/545) [0.0, 1.2]	2.8% (25/894) [1.7, 3.9]
	12 Months	8.5% (4/47) [0.5, 16.5]	13.3% (38/285) [9.4, 17.3]	1.3% (3/227) [0.0, 2.8]	8.1% (45/559) [5.8, 10.3]
Reintervention for Thrombosis	1 Month	0.0% (0/54) [0.0, 0.0]	0.3% (1/308) [0.0, 1.0]	0.0% (0/622) [0.0, 0.0]	0.1% (1/984) [0.0, 0.3]
	6 Months	0.0% (0/51) [0.0, 0.0]	0.3% (1/298) [0.0, 1.0]	0.0% (0/545) [0.0, 0.0]	0.1% (1/894) [0.0, 0.3]
	12 Months	0.0% (0/47) [0.0, 0.0]	0.4% (1/285) [0.0, 1.0]	0.0% (0/227) [0.0, 0.0]	0.2% (1/559) [0.0, 0.5]
Cardiovascular Hospitalization	1 Month	1.9% (1/54) [0.0, 5.4]	0.0% (0/308) [0.0, 0.0]	0.8% (5/623) [0.1, 1.5]	0.6% (6/985) [0.1, 1.1]
	6 Months	5.9% (3/51) [0.0, 12.3]	5.7% (17/298) [3.1, 8.3]	5.1% (28/547) [3.3, 7.0]	5.4% (48/896) [3.9, 6.8]
	12 Months	8.5% (4/47) [0.5, 16.5]	9.1% (26/285) [5.8, 12.5]	14.9% (37/249) [10.4, 19.3]	11.5% (67/581) [8.9, 14.1]
Major Vascular Complications[4]	1 Month	3.7% (2/54) [0.0, 8.7]	4.2% (13/308) [2.0, 6.5]	0.6% (4/623) [0.0, 1.3]	1.9% (19/985) [1.1, 2.8]
	6 Months	3.8% (2/52) [0.0, 9.1]	5.4% (16/298) [2.8, 7.9]	0.7% (4/546) [0.0, 1.4]	2.5% (22/896) [1.4, 3.5]
	12 Months	4.2% (2/48) [0.0, 9.8]	6.3% (18/285) [3.5, 9.1]	1.7% (4/230) [0.0, 3.4]	4.3% (24/563) [2.6, 5.9]

[1] The composite event is all-cause death at 30 days, and amputation, index-limb re-intervention, or index-limb-related death.
[2] Based on asymptotic Likelihood Ratio test. CIs for groups and difference are asymptotic.
[3] Deaths adjudicated by the CEC. In the continued access cohort, 2 additional deaths have occurred that are not yet adjudicated, for a cumulative total of 3 deaths.
[4] Major Vascular Complication is defined as serious Hematoma at access site >5 cm, False aneurysm, AV fistula, Retroperitoneal bleed, Peripheral ischemia/nerve injury, Any transfusion required will be reported as a vascular complication unless clinical indication clearly other than catheterization complication, Vascular surgical repair.

6.8 Mortality

Deaths for LEVANT 2 randomized and roll-in patients are summarized in Section 5.14. There have also been 3 deaths in the CA cohort, 2 of which have not been adjudicated. Both were site-reported as non-cardiac and not related to device or study procedure. One was CEC adjudicated as non-cardiac not related study procedure or device.

6.9 Safety Summary (All DCB Cohort)

No new safety concerns have been identified in the registry study of 657 additional patients treated with Lutonix DCB. In the randomized study (see Section 5.13), adverse events for Lutonix DCB were generally comparable to control PTA, and the observed frequency is comparable to what would be expected for the enrolled population based on historic data (see Section 0). Nevertheless, for a few adverse events the trend appeared unfavorable for Lutonix DCB. Select serious adverse events of potential interest are shown in Table 49 below through 12 months. Note that this table differs from those of Section 5.13, in which all events were reported for the randomized cohort through 24 months. Events that occurred between 12 and 24 months are not included below for comparability to the continued access data.

As shown in Table 49, none of the p values for a difference between Lutonix DCB and control PTA approaches significance. In every case the rate observed for all DCB lies within the 95% confidence interval of control PTA, and in most cases, the 95% CI of the DCB rate includes the rate observed for control, except when no events occurred in the control PTA group. Although the continued access study provides additional confidence in the adverse event rate for Lutonix DCB, it cannot improve confidence in the rate for control, which has a sample size limited by the 2:1 allocation ratio of the randomized cohort. Furthermore, these interim results must be interpreted with caution, since 12 month follow-up is incomplete and not all events have been adjudicated. Therefore, a discussion of historic rates for populations generally comparable to that enrolled in LEVANT2 is also provided (Section 0).

None of these events in Table 49 below were adjudicated by the CEC as possibly, probably or highly probably device or procedure related.

Table 49: Selected Serious Adverse Events (of Interest from the randomized study) for All DCB and PTA Cohorts through 12 Month Window

SAE (CEC) Event code	DCB Roll-in N=56 %(n)	DCB CA N=657 %(n)	DCB Randomized N=316 %(n)	All DCB N=1029 %(n)	All DCB Asympt 95%CI	Control PTA N=160 %(n)	Control PTA Asympt 95% CI	Exact P (Δ All DCB-PTA)
Angina	5.4%(3)	0.9% (6)	4.1% (13)	2.1% (22)	1.3, 3.0	1.3% (2)	0.0, 3.0	0.76

SAE (CEC) Event code	DCB Roll-in N=56 %(n)	DCB CA N=657 %(n)	DCB Randomized N=316 %(n)	All DCB N=1029 %(n)	All DCB Asympt 95%CI	Control PTA N=160 %(n)	Control PTA Asympt 95% CI	Exact P (Δ All DCB-PTA)
COPD	0.0% (0)	0.3% (2)	1.6% (5)	0.7% (7)	0.2 ,1.2	0.6% (1)	0.0, 1.9	1.00
CHF	0.0% (0)	0.0% (0)	1.9% (6)	0.6% (6)	0.1, 1.0	0.0% (0)	NA	1.00
Stroke	0.0% (0)	0.0% (0)	2.8% (9)	0.9% (9)	0.3, 1.4	0.6% (1)	0.0, 1.9	1.00

In addition to the events summarized above in Table 49, other adverse events of potential interest based on the randomized cohort include the rates of access site complications, hematoma, pseudoaneurysm, and hemorrhage. Since there is redundancy in event reporting (multiple events e.g. hematoma and bleeding requiring transfusion with one complication), these are best summarized in the composite secondary endpoint Major Vascular Complications, which is shown below in Table 50 for all DCB cohorts and control PTA at each time point.

In both analyses, the confidence intervals broadly overlap at all time points. Thirty-day follow-up in the Continued Access study is complete, and all of the observed difference between groups occurred within the 1 month window (there were 5 events in both the randomized DCB group and the control PTA group between 1 and 12 month visits). Safety with respect to major vascular complications is similar for Lutonix DCB and control PTA.

Table 50: Major Vascular Complications, All DCB Cohorts and Control PTA

	Visit	Roll-in DCB %(n/N) [95% CI]	Randomized DCB %(n/N) [95% CI]	Continued Access %(n/N) [95% CI]	All DCB %(n/N) [95% CI]	Control PTA %(n/N) [95% CI]
Major Vascular Complications[1] (CEC)	1 Month	3.7% (2/54) [0.0, 8.7]	4.2% (13/308) [2.0, 6.5]	0.6% (4/623) [0.0, 1.3]	1.9% (19/985) [1.1, 2.8]	1.3% (2/156) [0.0, 3.0]
	6 Months	3.8% (2/52) [0.0, 9.1]	5.4% (16/298) [2.8, 7.9]	0.7% (4/546) [0.0, 1.4]	2.5% (22/896) [1.4, 3.5]	2.6% (4/152) [0.1, 5.2]
	12 Months	4.2% (2/48) [0.0, 9.8]	6.3% (18/285) [3.5, 9.1]	1.7% (4/230) [0.0, 3.4]	4.3% (24/563) [2.6, 5.9]	4.9% (7/142) [1.4, 8.5]

[1]Major Vascular Complication is defined as serious Hematoma at access site >5 cm, False aneurysm, AV fistula, Retroperitoneal bleed, Peripheral ischemia/nerve injury, Any transfusion required will be reported as a vascular complication unless clinical indication clearly other than catheterization complication, Vascular surgical repair.

6.10 Discussion of Cardiovascular SAEs Reported Historically

LEVANT 2 was a randomized study, and all endpoints and events are assessed by direct comparison between randomized Lutonix DCB and control PTA groups. The study was sufficiently powered to test the primary safety and efficacy endpoints, and both endpoints were successful. Given the limited sample size of the control group (allocated 2:1) and the multiplicity of adverse events reported, it is not surprising that differences between certain event rates may be observed. Therefore, a brief discussion of outcomes reported in the literature for a generally comparable population is provided.

LEVANT 2 enrolled patients with symptomatic peripheral arterial disease (PAD) in need of treatment to restore patency in an occluded femoropopliteal artery. The most similar studies, RESILIENT [15, 35] and ZILVER [16], did not report event rates for stroke, CHF, angina, COPD, or cardiovascular hospitalizations.

As shown in Table 44 above, baseline characteristics of LEVANT 2 patients were generally comparable to the cohort with established PAD in the > 65,000 patient Reduction of Atherothrombosis for Continued Health (REACH) registry [31]. However, PAD patients enrolled in REACH did not undergo an invasive endovascular procedure at baseline; rather, events and treatments for the general population with established PAD were followed over time. There are certainly other important differences, and the results cannot therefore be directly compared to those of LEVANT 2.

The REACH study enrolled patients with cardiovascular risk factors (established PAD, CAD, or CVD; or ≥ 3 risk factors) in >5000 sites in 44 countries, and about 2/3 were enrolled in the US and Western Europe. Results at 1 year were reported separately for each cohort (PAD, CAD, CVD, or multiple risks)[34]. The subsets overlap, and (like LEVANT 2) about half of the REACH PAD cohort also had CAD. The evaluable cohort of patients with established (symptomatic/treated) PAD included 8581 patients. Cardiovascular events for this cohort are summarized in Table 51.

The adverse event rates observed for randomized DCB do not appear higher than those reported historically for the general symptomatic PAD population. For example, the stroke rate is similar and the rate of hospitalizations for angina and CHF were observed more frequently in the PAD cohort of REACH than were observed for Lutonix DCB.

Table 51: CV Event Rates in the PAD cohort of the REACH Registry at 1 Year

1 Year CV Event	REACH[34] Cohort with Established PAD (n = 8581)
All-cause mortality	3.76 (3.27-4.25)
CV death	2.51 (2.10-2.92)
Nonfatal MI	1.29 (1.01-1.58)
Nonfatal stroke	1.92 (1.56-2.27)
CV death, MI, or stroke	5.35 (4.77-5.97)
CV Death, MI, stroke, or cardiovascular hospitalization	21.14 (20.17-22.09)
Hospitalization for Unstable Angina	4.47 (3.97-4.97)
Hospitalization for CHF	4.36 (3.86-4.86)

6.11 Conclusion

Follow-up in the continued access registry is ongoing, and interim endpoint data is consistent with the randomized results. No new safety concerns have been identified, and based on interim data, the rates of adverse events of potential interest (e.g., angina, COPD, CHF, stroke, and major vascular complications) are observed less frequently in the larger population treated with Lutonix DCB.

7 LEVANT 1 RANDOMIZED CLINICAL STUDY

7.1 Summary

- LEVANT 1 enrolled 101 patients within balloon (n-75) and stent stratum (n-26) after predilatation. Within the balloon strata, 37 were randomized to Lutonix DCB and 38 were randomized to control PTA. Within the stent strata, 12 were randomized to Lutonix DCB and 14 were randomized to control PTA.
- Angiographic data at 6 months was evaluable for 74 patients, including 80% of the Lutonix DCB group and 67% of control PTA. The primary endpoint of mean Late Lumen Loss at 6 months favored Lutonix DCB (0.46±1.13) compared to control PTA (1.09±1.07), with a p-value of 0.016.
- At completion of the study, the percentage of enrolled patients with any death, amputation, or target vessel thrombosis was 8% (4/49) in the Lutonix DCB group compared to 12% (6/52) with control PTA.
- Through study completion at 24 months follow-up, a total of 35 patients in the ITT population had a CEC-adjudicated TLR, including 36% (15/42) in the Lutonix DCB arm and 49% (20/41) in the control PTA arm.
- Functional improvement was observed in both groups. Rutherford classification improved at 6, 12 and 24 months. Walking performance based upon the walking impairment questionnaire also improved from baseline at 6, 12 and 24 months in both groups.

7.2 Study Design

Levant I was a prospective, multicenter, single blind, randomized controlled clinical trial comparing the safety and efficacy of the Lutonix DCB to control PTA. As in LEVANT 2, patients presenting with clinical evidence of claudication or critical limb ischemia and an angiographically significant lesion in the femoropopliteal arteries were enrolled. Subject inclusion and exclusion criteria were similar to those in LEVANT 2 with lesion length between 4-15 cm and vessel diameter 4-6 mm.

After predilatation, patients were stratified to either the balloon group or the stent group (Figure 21). Patients were then randomized to either the Lutonix DCB or control PTA within the balloon or stent strata. Balloon sizes studied were 5 mm and 6 mm and the balloon lengths were 60 mm and 100 mm

For subjects randomized to the Lutonix DCB, the Investigator determined the appropriate size of by visual estimate. Investigators were instructed to inflate the Lutonix DCB within 3 minutes of insertion with a minimum inflation time of 30 seconds. For subjects randomized to the control PTA, the Investigator followed standard procedure for such a treatment utilizing a standard off-the shelf CE-marked PTA balloon. The Investigator determined by visual assessment the appropriate size of the balloon to be used.

Clinical follow-up was conducted at 1, 6, 12 and 24 months. DUS was performed at 6, 12 and 25 months. The CEC is comprised of three clinicians with expertise in vascular intervention who were not participants in the study reviewed and adjudicated all clinical events.

The primary endpoint was late lumen loss at 6 months as assessed angiographically. Prespecified secondary endpoints included the following:

- Safety - Device related adverse events at 30 days
- Primary patency of treated segment at 6, 12 and 24 months
- Target Lesion Revascularization (TLR) at 6, 12 and 24 months
- Target Vessel Revascularization (TVR) at 6, 12 and 24 months
- Device Success
- Procedural Success
- Change in ankle-brachial index (ABI) from pre-procedure to 6, 12, 24 month follow-up
- Change in Rutherford classification from pre-procedure to 6, 12, 24 month follow-up
- Changes in Walking Impairment Questionnaire results from pre-procedure to 6, 12, 24 month follow-up

The primary analysis was conducted the ITT population defined as all randomized patients. For assessment of the primary endpoint, stratification groups are pooled and late lumen loss of subjects randomized to Lutonix DCB and control PTA groups were compared using descriptive statistics. A sample size of one hundred subjects was expected to provide ≥80% power to detect a clinically meaningful difference in late lumen loss of 15% of RVD between treatment groups based on a 2-sample t-test with 2-sided $\alpha \leq 0.05$.

7.3 Inclusion Criteria

Clinical Criteria

- Male or non-pregnant female ≥18 years of age. Women of childbearing potential must have had a negative pregnancy test within 7 days of the procedure
- Rutherford Clinical Category 2-5
- Subject willing to provide informed consent and comply with the required follow-up visits, testing schedule, and medication regimen

Angiographic Criteria

- A single de novo or restenotic atherosclerotic lesion >70% by visual estimate in the SFA or popliteal artery ≥4 cm and ≤15 cm in total length.
- Target vessel diameter ≥4 mm and ≤6 mm
- Successful wire crossing of lesion
- A patent inflow artery free from significant lesion (>50% stenosis) as confirmed by angiography (treatment of target lesion acceptable after successful treatment of inflow artery lesions)

Subjects were excluded if any of the following conditions applied:

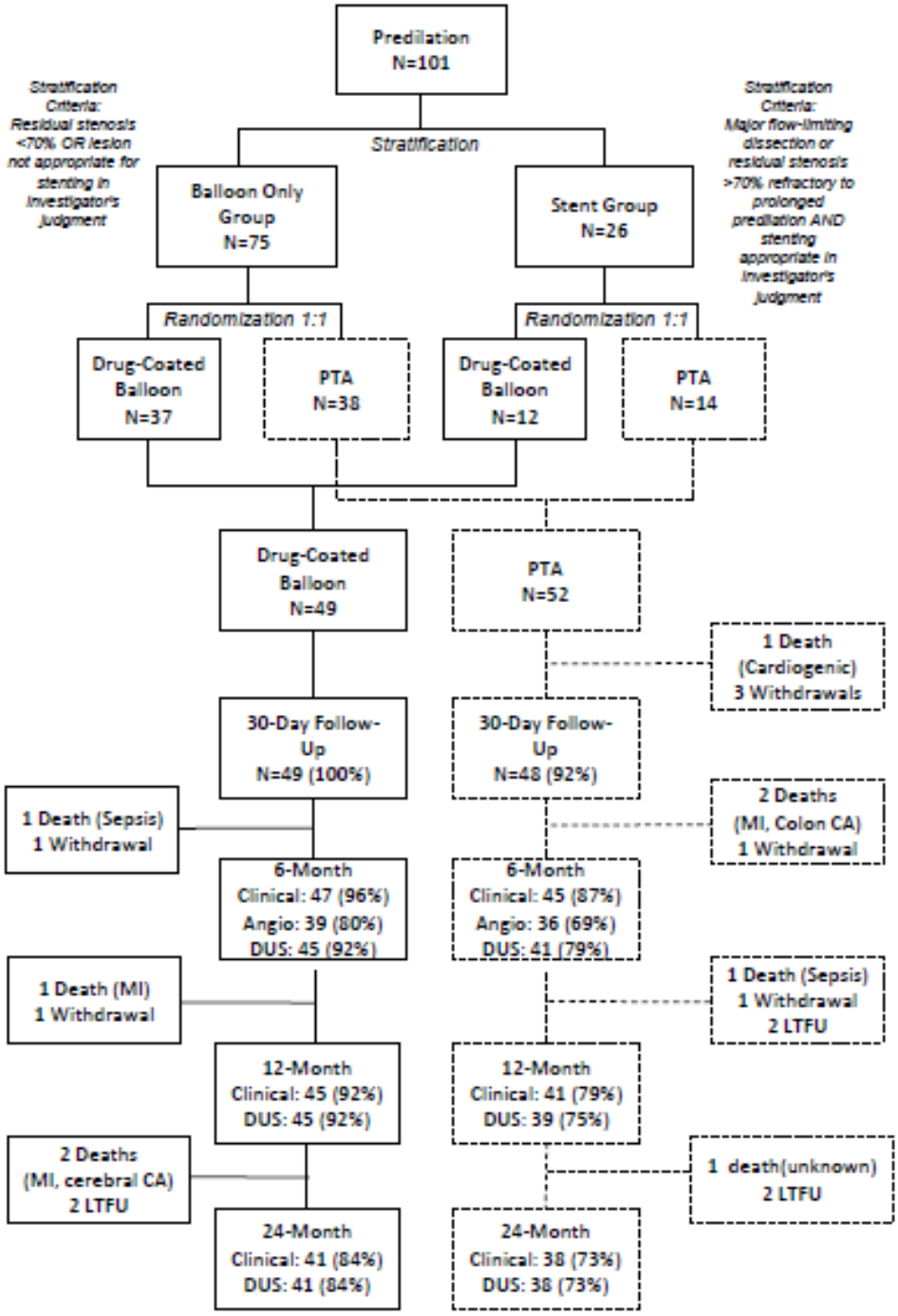
- Pregnant or planning on becoming pregnant in < 2yrs
- Life expectancy of <2 years
- Subject participating in an investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints.
- History of hemorrhagic stroke within 3 months
- Previous or planned surgical or interventional procedure within 30 days of index procedure
- Chronic renal insufficiency with creatinine >2.5 mg/L
- Prior surgery of the target lesion
- Inability to take required study medications
- Anticipated use of IIb/IIIa inhibitor prior to randomization
- Lesion length <4 cm or >15 cm or no normal proximal arterial segment for duplex US velocity ratios measurement
- Known inadequate distal outflow (A patent popliteal artery free from significant lesion (>50% stenosis) with at least one patent single vessel run-off as confirmed by angiography)
- Significant inflow disease
- Acute or sub-acute thrombus in target vessel
- Severe lesion calcification
- Acute vessel occlusion or sudden symptom onset
- Use of adjunctive therapies (e.g. laser, atherectomy, cryoplasty, scoring/cutting balloon)
- Prior participation in this study

7.4 Subject Disposition

The consort flow diagram in Figure 21 summarizes patient randomization, disposition, and evaluable follow-up on an ITT basis. Of the 101 patients meeting eligibility criteria after predilatation, 75 were randomized in the balloon only stratum with 26 randomized in the stent stratum. In the balloon only stratum, 37 and 38 were randomized to Lutonix DCB and control PTA, respectively. In the stent stratum, 12 and 14 were randomized to Lutonix DCB and control PTA, respectively.

Of the 101 patients randomized, 86 had 12 month clinical follow-up, including 92% (45/49) Lutonix Catheter and 79% (41/52) in the control PTA group. Six patients died (2 Lutonix DCB and 4 control PTA), 7 withdrew consent (2 Lutonix DCB, 5 control PTA), and 2 were lost to follow-up (both control PTA). Of the 101, 79 had 24 month follow-up, including 84% (41/49) Lutonix DCB and 73% (38/52) control PTA. Between 12 and 24 months, three additional patients died (2 Lutonix DCB, 1 control PTA), and 4 were lost to follow-up (1 Lutonix DCB, 3 control PTA).

Figure 21: LEVANT 1 Study Patient Flowchart



7.5 Demographics and Baseline Characteristics

The mean age of enrolled patients was 68±9 years with 63% male, 35% were current smokers, 34% were previous smokers and 48% had Type II diabetes mellitus. At baseline examination, 71% of the patients were rated a Rutherford Category 3, 22% were Rutherford Category 2, and the remaining 7% were Rutherford Category 4 and 5. More than 40% reported previous coronary artery disease, and other co-morbidities (renal disease, congestive heart failure, cerebrovascular disease and structural heart disease) were common. There were no statistically significant differences between the groups for any demographic or medical history factor.

By quantitative vascular angiography (QVA), mean lesion length was 8.1±3.7 and 8.0±3.8 cm and RVD was 4.1±0.6 and 4.2±0.7 mm in the Lutonix DCB and control PTA groups, respectively. Eighty nine percent of treated lesions were de novo lesions, with the majority located in the mid and distal portions of the SFA. Popliteal lesions were treated in 4 (8.2%) test and 3 (5.8%) control cases.

The overall rate of concomitant stent implantation and procedural characteristics were similar in both randomized groups.

7.6 Primary Endpoint

Angiographic data was evaluable for 74 patients, including 80% of the Lutonix DCB group and 67% of control PTA. The primary endpoint of mean Late Lumen Loss at 6 months favored the Lutonix DCB arm (0.46±1.13) compared to the control PTA arm (1.09±1.07), with a p-value of 0.016.

The difference in mean late loss between arms in the balloon-only stratification group was also lower for the Lutonix Catheter (0.45±1.18 vs. 1.19±1.15, p=0.024). The difference between arms was not significant in the stent group, with late loss of 0.49 ± 1.01 for Lutonix DCB vs. 0.90 ± 0.91 for control PTA, p = 0.373.

7.7 Secondary Endpoints

Through study completion at 24 months follow-up, the percentage of enrolled patients with any death, amputation, or target vessel thrombosis was 8% (4/49) in the Lutonix DCB group compared to 12% (6/52) in the control group.

Deaths in the Lutonix DCB arm were due to cancer (1), sepsis (1), and cardiac (2). Deaths in the control PTA arm were due to cancer (1) and cardiac (4). There were no target vessel thromboses and 1 amputation (subject later died) in the Lutonix DCB arm and one target vessel thrombosis (subject later withdrew) in the control PTA arm. Composite major adverse events were 39% (19 of 49) in the Lutonix DCB group, including 15 TLRs, 1 amputation, and 4 deaths vs. 46% (24 of 52) for control PTA, with 20 TLR, 1 thrombosis, and 5 deaths.

At 24 months, a total of 35 patients in the ITT population had a CEC-adjudicated TLR, including 36% (15/42) in the Lutonix DCB arm and 49% (20/41) in the control PTA arm (Table 52). Only one patient had a TVR without having a TLR, for a TVR rate of 36% (15/42) in the Lutonix DCB arm compared to 51% (21/41) with control PTA.

Table 52: LEVANT 1 Cumulative Adverse Events as Adjudicated by CEC

Adverse event type through Designated Follow Up ***(number of patients having any events and total number of events)***	**Through 12 Months**		**Through 24 Months**	
	Lutonix DCB N=49 n (total events)	**Control PTA N=52 n (total events)**	**Lutonix DCB N=49 n (total events)**	**Control PTA N=52 n (total events)**
Non-serious AE[1]	23 (32)	29 (51)	28 (50)	31 (74)
SAE[1]	33 (66)	34 (80)	39 (90)	39 (110)
Thrombosis (target vessel)	0 (0)	1 (1)	0 (0)	1 (1)
Amputation	1 (1)	0 (0)	1 (1)	0 (0)
Death	3 (3)	4 (4)	4 (4)	5 (5)
TLR	13 (17)	14 (14)	15 (20)	20 (21)
TVR	13 (17)	15 (19)	15 (20)	21 (26)

[1] Any given patient may have more than one reported AE or SAE. SAEs reported at 24 Months follow-up that occurred within the 12 Month follow-up time window (395 days) are included at 12 Months.

Table 53: LEVANT 1 Target lesion revascularization, 12 and 24 months

Subgroup	**12 Months**		**24 Months**	
	Lutonix DCB % (n/N)	**Control PTA % (n/N)**	**Lutonix DCB % (n/N)**	**Control PTA % (n/N)**
ITT	28.9% (13/45)	33.3% (14/42)	35.7% (15/42)	48.8% (20/41)
Balloon-only Strata	35.3% (12/34)	34.5% (10/29)	43.8% (14/32)	50.0% (14/28)
Stent Strata	9.1% (1/11)	30.8% (4/13)	10.0% (1/10)	46.2% (6/13)

Twenty-four month primary patency (PSVR < 2.5 without TLR) was 54% (22/41) for Lutonix Catheter compared to 32% (12/38) for control POBA, p = 0.047 (Table 54).

Table 54: Primary Patency (DUS ≥ 2.5) at 12 and 24 months (success must be proven by DUS, methods of Levant 2 analysis)) - ITT

Threshold for Restenosis Subgroup	12 Months		24 Months	
	Lutonix DCB % (n/N)	Control PTA % (n/N)	Lutonix DCB % (n/N)	Control PTA % (n/N)
DUS PSVR ≥ 2.5	65.1% (28/43)	52.5% (21/40)	53.7% (22/41)	31.6% (12/38)
Balloon-only Strata	59.4% (19/32)	50.0% (14/28)	45.2% (14/31)	35.7% (10/28)
Stent Strata	81.8% (9/11)	58.3% (7/12)	80.0% (8/10)	20.0% (2/10)

Functional improvement was observed in both groups. Rutherford classification improved at 6, 12 and 24 months. Walking performance based upon the walking impairment questionnaire also improved similarly from baseline at 6, 12 and 24 months in both groups.

8 Lutonix Global SFA Registry

8.1 Summary of Findings

- The study is actively enrolling, with 437 patients enrolled as of February 24, 2014 export.
- 340 patients have completed 1 month and 126 patients have completed 6 month follow-up.
- Endpoints are not analyzed at this time since only 7 patients have completed 12 month follow-up.
- Site-reported AEs and SAEs are consistent with safety of the Lutonix DCB in real world use. No unexpected adverse events have been observed.

8.2 Study Design and Endpoints

The Lutonix® Global SFA Registry is a post-market registry intended to demonstrate safety and assess the clinical use and outcomes of the Lutonix DCB in a heterogeneous patient population in real world clinical practice. The study will enroll up to 1,000 patients with follow up for a minimum of 2 years.

This registry is performed with marketed devices within the indications for use, and each site is to follow routine medical practice when examining patients and using the Lutonix DCB as detailed in the IFU packaged with the device. Aside from providing 5 year informed consent, collection and analysis of patient data, and required follow-up, all treatments are per standard of care. The study follow up schedule requires either telephone contact or clinical visits at 1, 6, 12 and 24 months after the index procedure.

Primary endpoints:

Efficacy: Freedom from TLR at 12 months.

Safety: Freedom at 30 days from TVR, major index limb amputation, and device- and procedure-related death

Secondary endpoints:

- Acute Device and Procedural success
- Primary patency at 6, 12 and 24 months (site-reported)
- Freedom separately from each of the following adverse events at 30 days and at 6, 12, and 24 months:
  - All-cause death
  - Device- and procedure-related mortality
  - Unexpected device or drug-related adverse events
  - Index limb amputation (major and minor reported separately)

- Reintervention for treatment of thrombosis of the target vessel
- Reintervention for embolization to its distal vasculature
- Target Lesion Revascularization (TLR)
- Target Vessel Revascularization (TVR)
- Composite of all-cause perioperative (≤30 day) death and from the following: index limb amputation, index limb re-intervention, and index-limb-related death

Inclusion Criteria:

1. Male or non-pregnant female ≥18 years of age;
2. Rutherford Clinical Category ≤ 4;
3. Patient is willing to provide 5-year informed consent and comply with the required follow up;
4. Stenotic or obstructive vascular lesions of the femoropopliteal artery;
5. Lesion(s) can be treated with available Lutonix® Drug Coated PTA Dilatation Catheter device size matrix per current IFU;
6. At least one patent native outflow artery to the ankle free from significant lesion (≥50% stenosis) as confirmed by angiography (treatment of outflow disease is NOT permitted; treatment of in-flow disease is permitted prior to treatment with the Lutonix® Drug Coated PTA Dilatation Catheter).

Exclusion Criteria:

1. Patient is currently participating in an investigational drug or device study;
2. Inability to take recommended medications as stated in the IFU or non-controllable allergy to contrast;
3. Pregnant or planning on becoming pregnant or men intending to father a child;
4. Rutherford Class > 4
5. Known inadequate distal outflow or planned future treatment of vascular disease distal to the target lesion.

8.3 Current Status of Enrollment and Follow-up

Enrollment began December 11, 2012 and is ongoing. As of a database export on February 24, 2014, four hundred thirty seven (437) patients had enrollment data in the database.

As shown in Table 55, 340 patients have completed 1 month follow-up and 126 patients have completed 6 month follow-up. Mean days in study (calculated as days from procedure to termination or last follow-up visit date) is 71.4 ± 82.2 days.

Table 55: Subject Disposition by Visit Window

Visit Interval	Disposition	% (n/N)
1 Month	Exited	0.2% (1/437)
	Had visit	77.8% (340/437)
6 Months	Exited	0.9% (4/437)
	Had visit	28.8% (126/437)
12 Months	Exited	1.1% (5/437)
	Had visit	1.6% (7/437)

8.4 Baseline and Procedural Characteristics

The currently enrolled population is age 68; 68% are male, 37% are current smokers, 66% have dyslipidemia, 41% have hypertension, 24% have prior CAD, and 13% have a history of MI. The majority (61%) were Rutherford Class 3, while 7% had critical limb ischemia; mean pre-procedural ABI was 0.7.

Mean lesion length was 105 mm. Lesions had 90% diameter stenosis (%DS) and reference vessel diameter 5.2 mm. Lesions were TASC II Type C and D in 17% of cases; 29% were popliteal, 32% were calcified, and 31% were totally occluded.

Predilation was performed 58% of the time, and an average of 1.6 Lutonix DCBs were used. Provisional stents were placed in 11% of cases. The final post-procedural %DS was 20%.

8.5 Safety Evaluation

All site-reported serious adverse events are shown in Table 56. To date, the most frequent SAEs are Pseudo aneurysm (0.7%, 3/437) and Occlusion/Closure (0.7%, 3/437). None of these were device related. No unexpected adverse events have occurred.

Table 56: Summary of Serious Adverse Events (SAEs)

AE Code	AE Sub-Code	Number of Events	Percent of Patients (n/N)
01 Access site complication	0101 Arterial embolizations	2	0.5% (2/437)
	0102 Arterial occlusion puncture site	1	0.2% (1/437)
	0104 Hematoma/ bleeding puncture site - major	1	0.2% (1/437)
	0107 Pseudo aneurysm	3	0.7% (3/437)
	0108 Puncture site infection	1	0.2% (1/437)
02 Cardiovascular	0202 Angina, stable	1	0.2% (1/437)
	0203 Angina, unstable	1	0.2% (1/437)
	0210 Death	1	0.2% (1/437)
04 Gastrointestinal	0402 Cholecystitis	1	0.2% (1/437)
	0406 Gastritis	1	0.2% (1/437)
06 Neurological / nervous system	0608 Peripheral nervous system complication	1	0.2% (1/437)
07 Respiratory	0702 Carcinoma	1	0.2% (1/437)
	0708 Other respiratory	1	0.2% (1/437)
	0709 Pneumonia	1	0.2% (1/437)
08 Skeletal, spine and muscular system	0804 Fracture (bone)	2	0.5% (2/437)
	0806 Osteomyelitis	1	0.2% (1/437)
10 Target lesion	1005 Occlusion/ closure	3	0.7% (3/437)
11 Target vessel	1101 Aneurysm	1	0.2% (1/437)
	1105 Occlusion/ closure	1	0.2% (1/437)
12 Genito-urinary system	1205 Renal failure/ insufficiency	1	0.2% (1/437)
13 Various	1302 Amputation	1	0.2% (1/437)
	1305 Death (non - cardiac or neurological)	1	0.2% (1/437)
	1312 Other	1	0.2% (1/437)
	1314 Claudication	1	0.2% (1/437)
14 Vessel specific complications (not puncture site or target vessel)	1405 Dissection	1	0.2% (1/437)
	1406 Embolism	1	0.2% (1/437)

9 Post-Approval Plan

The LEVANT 2 Randomized study has enrolled 372 Lutonix DCB patients (56 roll-in and 316 randomized) and 160 control PTA patients. The LEVANT 2 Continued Access & Safety Registry studies have enrolled an additional 657 Lutonix DCB patients.

For post-approval, the combined total of 1029 patients will be followed for 5 years.

The prespecified primary endpoint is the rate of unanticipated device- or drug-related adverse events over time through 60 months. Two secondary endpoints of the LEVANT 2 Continued Access/Safety Registry will have hypothesis tests. The hypothesis test for the safety endpoint is noninferiority of composite safety at 12 months (same as the primary safety endpoint of the LEVANT 2 Randomized study) comparing the LEVANT 2 Continued Access/Safety Registry cohort against the control PTA cohort from the LEVANT 2 Randomized study. The hypothesis test for the secondary efficacy endpoint is superiority of primary patency at 24 months comparing the combined Lutonix DCB cohort from the LEVANT 2 Randomized study and the LEVANT 2 Continued Access against the control PTA cohort from the LEVANT 2 Randomized study.

In addition, up to 1000 patients will be enrolled in the real-world registry (Lutonix Global SFA Registry). These patients will be followed for 2 years and provide additional supportive safety and efficacy experience after treatment with Lutonix DCB.

10 Benefit Risk Conclusion

Summary

The Lutonix DCB is an angioplasty balloon coated with paclitaxel. Like all angioplasty balloons, the immediate result of treatment is the opening of the blocked artery by mechanical dilatation. The additional benefit of the paclitaxel drug coating is to improve the durability of patency of angioplasty by reducing restenosis over time without leaving a prosthetic implant behind.

The LEVANT 2 trial is an ongoing prospective, multicenter, single blind, randomized, controlled trial of 476 randomized subjects. The procedural success of Lutonix DCB was comparable to that of control balloon angioplasty (88.9% vs. 86.8%). In addition, at 12 months, primary patency of the Lutonix DCB group was superior to that of the angioplasty control group (65.2% vs. 52.6%, p = 0.015). Primary Safety (freedom from 30-day all cause perioperative death and 12-month index limb-related death, amputation, and revascularization) of DCB was non-inferior to uncoated control PTA (83.9% vs. 79.0%, p = 0.005). These results demonstrate improved patency over time without introducing new safety concerns. Additionally, by several clinical and quality of life measures, there is significant benefit to patients post procedure with durable results through the follow-up period and numerically superior results to standard PTA. On a comparative basis with standard PTA, the Lutonix DCB provided statistically significant improvement in the walking distance portion of the WIQ (Walking Improvement Questionnaire) and a statistically significant post hoc improvement in Rutherford Class without reintervention. These results demonstrate a favourable benefit to risk comparison.

Clinical Context and Unmet Need

PAD, a subgroup of cardiovascular disease, affects 10% of Americans and 20% of Americans over the age of 70 and is a cause of major morbidity. Lower limb PAD is a progressive disease that often presents with intermittent claudication resulting in reduced quality of life (QoL) owing to pain in the legs on exercise, or with more severe symptoms of critical limb ischemia. In addition to QoL, exercise is a critical lifestyle component for the management of cardiovascular disease, and claudication pain often interrupts normal activity thus exacerbating the disease process. As such, restoration of flow is often required to help PAD patients resume normal activity.

Angioplasty is the standard of care for treatment of femoropopliteal artery lesions. PTA is the primary treatment recommendation in the ACC/AHA guideline, with stents used only “as salvage therapy for a suboptimal or failed result from balloon dilatation (e.g., persistent translesional gradient, residual diameter stenosis greater than 50%, or flow-limiting dissection)”[17, 18]. Although still considered the standard of care, a meta-analysis of conventional PTA at 12 months reported primary patency as low as 33% [7]. As such, primary treatment with bare nitinol or paclitaxel-eluting stents has become more common with primary patency rates range from 67-80% at 12 months [12-16].

Balloons and stents have provided evolutionary improvements in the treatment of femoropopliteal stenoses, but the problem of restenosis, which begins immediately after these therapies, persists and can be exacerbated by stents. Stents provide a scaffold to prevent abrupt vessel closure and allow overstretching the vessel beyond its native diameter, but their outcomes in the femoropopliteal artery are complicated by chronic exposure to the mechanical torsion, flexion, compression, and extension of lower extremity vessels and the possibility of stent fracture [19, 20]. Implantation of a stent can also cover (i.e., "jail") collaterals and limit the treatment options available to the patient in the event repeat intervention or surgery becomes necessary. In addition, treatment of in-stent restenosis is particularly problematic. Therefore, a significant clinical need remains for a device that is able to achieve more durable patency than PTA but does not require a permanent implant. Lutonix DCB addresses this unmet need.

Secondary Endpoints

Clinical indicators in the trial included ABI (blood pressure index), Rutherford scores (categorization of symptomology), and walking impairment WIQ scores (categorization of functionality). Each of these significantly improved ($p < 0.001$) from before treatment to 12 months in both the DCB and PTA groups, with most point estimates numerically favoring Lutonix DCB. Improvement in the walking distance component of the WIQ demonstrated a significant difference between treatment groups at 12 months (DCB-PTA = 9.3; 95% CI [1.6, 17.0]). Additionally, at 12 months, 88.2% of Lutonix DCB patients and 82.4% of control PTA patients had improved Rutherford Class compared to baseline, indicating sustained benefit.

Although changes in QOL and functional parameters were similar for both groups, interpretation of these measures is complicated by interim reinterventions, comorbidities, and progressive disease in non-treated vessels. A post-hoc analysis of sustained improvement in Rutherford class without target vessel reintervention suggests a clinical benefit in favor of the DCB group compared to the control PTA group at 12 months (76.2% vs. 66.6%; p=0.041).

Freedom from TLR was numerically favorable for the Lutonix DCB group (87.7% for DCB vs. 83.2% for control PTA, $p = 0.208$), but no statistical difference between arms in Freedom from TLR rates was observed. It is worth noting that if bail-out stenting were to have been counted as a TLR in the same manner as previous stent studies, then a significant difference in Freedom from TLR (85.3% for test DCB vs. 76.4% for control, $p = 0.024$) would have been observed. TLR rates were impacted by the unique design elements of Levant 2, namely, the follow-up clinician was different from the clinician who initiated the index procedure, and, the follow- up clinician was blinded to be blinded to treatment arm and DUS imaging results at time of follow-up clinical assessment and made the decision to reintervene based on the clinical symptoms only. The potential subjectivity with the decision for reintervention, TLR, reinforces the importance of primary patency as an objective endpoint that which is adjudicated by the blinded, independent core lab.

Discussion of SAEs

Serious AEs that were adjudicated by the CEC to be probably or highly probably related to the study device were reported in 11.1% of Lutonix DCB subjects and 18.1% of PTA subjects. CEC-adjudicated procedure-related SAEs were reported in 15.2% of Lutonix DCB subjects and 21.3% of PTA subjects.

A few events (e.g., vascular complications, stroke, CHF, angina, COPD) trended unfavorably for Lutonix DCB in the randomized cohort. The observed event rates are consistent with those historically reported for the enrolled population with symptomatic PAD. Although only interim data is available, these events are observed less frequently in the larger population of the 657 patient single arm LEVANT 2 Continued Access/Safety study in which follow-up visits have been completed for 99% at 30 days, 82% at 6 months, and 35% at 12 months.

Seven subjects (2.4%) died in the DCB group compared to four (2.8%) in the control group through 12 months; none of these were adjudicated as related to the device, procedure, or index limb. There was a single major amputation (in the DCB group, adjudicated as not device related) and no minor amputations in either group. Through 12 months, freedom from reintervention for treatment of target vessel thrombosis or embolization to its distal vasculature was 99.6% for DCB compared to 99.3% for control PTA. Freedom from procedural embolism was 99.4% for DCB compared to 98.1% for control, consistent with the absence of any increase in embolic risk due to the drug coating.

Benefit Outweighs Risk

There is a growing PAD population in the US with multiple co-morbidities and a clinical need for a device that is able to achieve more durable patency than PTA without requiring a permanent implant. Unlike limitations with stents, a non-prosthetic based endovascular treatment allows clinicians to treat a broader patient population and preserves future treatment options.

The results from the randomized IDE study provide the pivotal clinical evidence supporting the safety and effectiveness of Lutonix DCB and additional safety data from the Levant 2 Continued Access Study further supports the safety of this technology. LEVANT 2 successfully met both co-primary (safety and efficacy) endpoints at 12 months by direct comparison to conventional balloon angioplasty. For both Lutonix DCB and control PTA, the immediate goal of treatment is to restore flow through a blocked artery. This was associated with a benefit in clinical and self-reported outcomes that was similar for both treatment groups, with numerical superiority in the DCB group. The differences significantly favoured Lutonix DCB in the walking distance component of the WIQ and in post hoc sustained improvement in Rutherford Class without reintervention. After 12 months, the primary patency rate for Lutonix DCB group was significantly higher than the primary patency rate for control PTA, demonstrating that treatment with Lutonix DCB is more effective than PTA.

The primary safety endpoint was also met, and there were comparable adverse event rates observed between the Lutonix DCB and standard PTA arms. There were no deaths related to either the procedure or device and there were no unanticipated adverse device effects. Interim 24-month and single arm data from the complimentary continued access study provides additional evidence supporting safety that alleviates concerns regarding differences in the safety profile. The totality of data suggests Lutonix DCB provides a clinical benefit with an acceptable safety profile compared to standard PTA. The benefit to risk comparison is favourable, with no implant (stent) left behind.

These results demonstrate that treatment of native femoropopliteal lesions with Lutonix DCB provides more durable patency than standard PTA through 12 months with comparable safety and provides a reasonable assurance of safety and effectiveness.

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